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Original Articles and Clinical Cases.

# THE CYTO-ARCHITECTURE OF THE CEREBRAL CORTEX OF A HUMAN FŒTUS OF EIGHTEEN WEEKS.

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## I.—INTRODUCTION.

OF late years much progress has been made in the study of the cyto-architecture of the cortex cerebri and of cerebral function. In 1905 and 1907, Campbell [6] and Brodmann [4] respectively published complete maps of the various areas into which the human adult cerebral cortex may be divided, and further details together with similar maps dealing with the cortex of certain orders of the mammalia have been published both by them and by other workers, notably by Mott [9], Mott and Kelley [10], Mott and Schuster [11 and 12], Watson [14].

As far as we are aware, however, no systematic study of the early evolution of the cyto-architecture of the human cortex cerebri has hitherto been attempted.



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On different occasions during the past twelve years, reference has been made by one of us (J. S. B.) to the characteristic features of the cortex of fœtuses and infants, and to the manner in which this structure becomes laminated and develops. In 1900 [1] a description was given of the cortex of the visual area (both visuo-sensory and visuo-psychic) of a child of 3 months, and of a case of anophthalmos of the age of 1 month. In both these cases the visuo-sensory area was mapped out. It was shown that in the case of the former the visuo-sensory area was relatively large in extent, though normal in distribution, whilst in the latter this area was deficient both in extent and in distribution, and its cortex exhibited a similar thinning of the outer layer of granules (Layer IIIa), and of the line of Gennari (Layer IIIb), to that which occurs in cases of long-standing blindness. It was further shown that an almost exact correspondence obtains between the thickness of the conjoined first and second layers of the cortex and the existing degree of amentia or dementia.

In 1903 [2] a description was given of the mode of development of the cortex of the prefrontal area, based on observations made on fœtuses of different ages, stillborn children and infants. It was shown that definite lamination appears in the prefrontal region at about the sixth month of fœtal life, by separation off of the innermost neuroblasts from the remainder. In other words the cortex develops from within outwards. When lamination is completed the cortex consists of the following five primary laminæ, of which two are mainly fibre-laminæ, and three mainly cell-laminæ: (1) *Outer fibre-lamina* or superficial layer; (2) *outer cell-lamina* or pyramidal layer of nerve-cells; (3) *middle cell-lamina* or layer of granule-cells; (4) *inner fibre-lamina* or inner line of Baillarger, and (5) *inner cell-lamina* or layer of polymorphic cells. These observations were confirmed by Watson in 1907 [14], and Brodmann's monograph which was published in the year 1909 [5] contains certain illustrations of fœtal cortex which agree in every histological respect with the features above referred to.

In 1910 [3] this description was amplified and elaborated, and it was pointed out that, whilst the cortex generally evolves from within outwards, that of the visuo-sensory area (sensory projection cortex) develops before that of the visuo-psychic zone (cortex of lower association), and the latter evolves before the cortex of the prefrontal region (cortex of higher association).

Whilst it is not necessary for our present purpose to give further details with regard to these investigations, it may be remarked that

in spite of their incompleteness they have served as a key for the elucidation of the structure of the cortex cerebri in the various types of mental disease, from the idiot on the one side of the scale to the dement on the other, and to enable a general pathology of mental disease to be indicated as a broad generalization of amentia and dementia on a basis of cortical sub-evolution and dissolution.

Though not germane to the subject, reference must not be omitted to the classical work of Flechsig [8] on cortical localization, since this has so largely served as the basis of the more modern researches in this subject. Whilst these myelinogenetic observations of Flechsig, and the more recent researches of the Vogts, have furnished valuable information for correlation with the results of the study of the cyto-architecture of the adult cortex, they are without bearing on the early evolution of the cerebral cortex, as lamination and histological differentiation occur at a much earlier date than does myelinization.

The observations on the mode of evolution of the cortex of the fœtus to which reference has just been made have enabled certain general laws of development to be stated. They are, however, not sufficiently complete to enable detailed statements to be made with regard to the early evolution of the cortex and to the histologically differentiable areas which first make their appearance.

## II.—Material and Methods.

We have endeavoured in the present research to fill this gap from the aspects both of cyto-architecture and of cortical localization. The facts which determined our choice of a brain for these purposes are as follows: In a fœtus of six months Betz-cells are present, and the prefrontal region, which is of very late development, has begun to laminate. In a fœtus of a little more than four months slight indications of differentiation of neuroblasts exist in the prefrontal region, but no definite evolution of lamination has occurred here.

For the study of the early evolution of the cyto-architecture of the human cerebrum, a brain, therefore, from a fœtus of about eighteen weeks—i.e., a trifle older than the last just referred to—seemed most likely to be productive of useful results.

The evidence on which is based the age of the fœtus we have employed is as follows:—

The fœtus when extended measured 25 cm. in length. When flexed as *in utero* the length from the vertex to the tip of the sacrum

was 14·25 cm. The fingers were distinct and separate, and the nails had appeared. The scalp was covered with downy hair, but no hair whatever was apparent on the body. The mouth was open. The membrana pupillaris was present. Ossification had not begun in the os calcis or in the pubic bone. Small centres of ossification were found in the upper two sacral segments. The gall-bladder was formed. It was relatively thick, and the cavity was small, but apparent. A slight

FIG. 1.—Two diameters. Unstripped left hemisphere of human fœtus of the age of eighteen weeks.

fold was noticeable at the ileocæcal junction, but the valve was not present. The kidneys were of about the size of a small hazel-nut, and measured 23 mm. in length by 8 mm. in width. The sex was definitely determinable, the fœtus being a female.

As at this age the brain, even when hardened, is of the consistence of soft jelly or blancmange, considerable difficulties were met with which, without proving unsurmountable, nevertheless rendered the study of the hemispheres less complete than was at first hoped. Unfortunately it is impossible in a research of this particular kind to

fill in the gaps by employing another exactly similar brain. This is the case on the one hand because it would, to say the least, be very difficult to duplicate a brain of a particular age; and on the other because, as one of us has experienced, great differences exist in the degree of development of two brains which are apparently of exactly the same age. These are in fact so marked as to render futile any attempt to fix in an exact manner the various stages of early cortical development.

The brain was hardened in formalin *in situ*, the skull bones of the vertex being first removed. After a preliminary hardening the brain was carefully floated into a separate dish of formalin. The examination was conducted by the only really satisfactory method in our experience, that of piecemeal blocking—the pia-arachnoid being retained as long as possible in order to keep the fragile hemispheres from breaking up, and the blocks being cut under fluid. The latter were embedded and cut in paraffin, and the sections were selected by counting and stained by the polychrome and iron-alum-hæmatoxylin methods. The former method was found to demonstrate the Betz-cells in a beautiful manner, whereas the latter was of value owing to the permanent nature of the results obtained by means of it, since it is quite easy with experience to interpret such sections in terms of the more elegant but less permanent polychrome specimens.

## III.—Anatomical Description of the Cerebrum.

The fissuration of the hemispheres under description agrees with the fœtal measurements already given in indicating an age of about eighteen weeks.

Externally the insula is very large, the fronto-parietal (superior frontal and parietal) operculum is nearly horizontal, and the (inferior) frontal operculum makes almost a right angle with the former anteriorly, and the temporal operculum one of full 60° with it posteriorly. The orbital surface of the frontal lobe, therefore, points almost directly forwards.

Above the posterior third of the fronto-parietal operculum and occupying the middle trisection of the external surface is a short *furrow of Rolando*, which is a distinct fissure in its upper part and a superficial groove in its lower. It is of interest that the Rolandic angle is almost a right angle.

The outer surface of the hemisphere is therefore much less developed than is that of Symington's [13] fifth-month fœtus, which shows a

smaller insula, a longer and more oblique furrow of Rolando, and also pits representing the superior and inferior precentral sulci and (?) the parallel.

On the internal aspect, part of the *sulcus cinguli* is present as a shallow ∧-shaped furrow. Posteriorly, the *stem* of the *calcarine fissure* is very evident in both hemispheres as a deep and distinct fissure. In the right hemisphere a (temporary) parieto-occipital fissure is well marked, and in the left a mere trace of the latter is present. The left hemisphere is thus (as is usual) slightly ahead of the right in its degree of evolution.

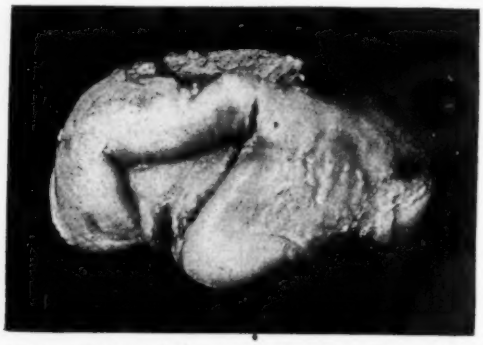

FIG. 2.—Natural size. Left hemisphere stripped. The cracks, and particularly the site near the upper edge from which blocks have been removed, indicate the fragile condition of the tissue.

Owing to the numerous descriptions of the calcarine fissure which are given by different anatomists, it is desirable to state that we here follow that given by one of us (J. S. B.) [1], under which it is described as consisting of three subdivisions—a *stem*, a *body* which consists of the two cuneo-lingual annectants and the part between them, and a *posterior extremity*. This subdivision of the fissure is justified for the purposes of description by the usual large size of the posterior cuneo-lingual annectant, and the frequency with which this is superficial, thus separating off the posterior extremity of the calcarine sulcus from the remainder. The primary division into a *stem* and a *posterior* portion is, however, the correct one, as it is founded on an earlier embryological basis.

In the brain under description, the *stem* is the portion of the fissure which is present.

The following brief account of the development of the calcarine fissure is derived from the classical description of Cunningham [7]. Towards the end of the second or the beginning of the third month of intra-uterine life the precursors of the parieto-occipital and calcarine fissures appear synchronously, and include the primitive cuneus. These primary parieto-occipital and calcarine fissures shortly afterwards disappear, leaving, however, intact the portion which later on becomes the stem of the calcarine sulcus, and which is thus one of the primary fissures of the cerebrum. "This portion alone assumes the responsibility of maintaining the intra-ventricular elevation which results in the calcar avis. Between the fifth and seventh months of intra-uterine life a secondary sulcus appears, as 'two' punctate depressions, one on the occipital pole and the other midway between this and the hinder part of the anterior calcarine fissure or stem. These deepen and then show a tendency to run towards each other in a horizontal direction." The anterior of these depressions soon becomes the deeper, and later on joins the stem, the point of junction being visible in adult life as the anterior cuneo-lingual annectant. The junction between the posterior depression and the rest of the fissure occurs much later, and in many adult brains, and commonly in the negro, the underdeveloped brains of certain of the insane, and the fœtus, it never takes place at all, the posterior extremity remaining usually as a short vertical fissure in the region of the pole of the hemisphere. When, as is usually the case, the junction takes place, the site of this is indicated in the adult brain by the posterior cuneo-lingual annectant gyrus.

The reason for this somewhat detailed description of the structure and mode of development of the calcarine fissure will become clear when the visuo-sensory area is under description, as this presents certain interesting features which can only be explained satisfactorily on developmental grounds.

In the following account of the results of our histological examination, we shall first indicate the limits of such cortical areas as we have been able to define, and shall then give a detailed description of the cyto-architecture of the cortex of these areas and of certain other regions in which it has been possible to recognize a differentiation of structure.

Under these respective headings we purpose to describe:—

(*a*) The limits of the Betz-cell and visuo-sensory areas.

(*b*) The cyto-architecture of

(1) The precentral (Betz-cell) cortex.

(2) The post-central cortex.
(3) The cortex of the visuo-sensory area.
(4) The cortex of (part of) the gyrus cinguli.
(5) The cortex of the anterior frontal region.

## IV.—The Localization of the Betz-cell Area.

The discovery of Betz-cells in a fœtus of eighteen weeks came as such a surprise that the fact that we were able with relative ease to map out the area containing them seemed commonplace.

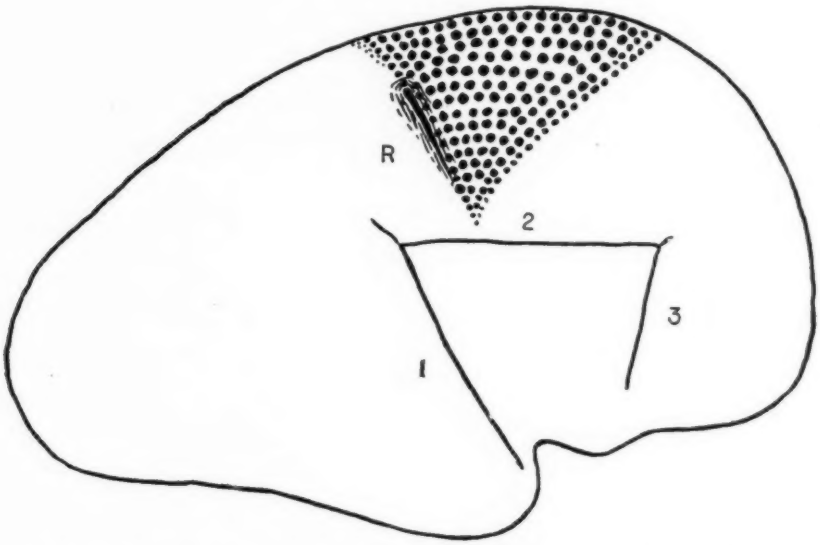


Fig. 3.—Two diameters. Outer surface of right hemisphere. The Betz-cell area is mapped out in dots. The small dots indicate where the area shades into the neighbouring cortex, a sharp line of demarcation existing elsewhere. R, furrow of Rolando: 1, temporal operculum; 2, fronto-parietal (superior frontal and parietal) operculum; 3, (inferior) frontal operculum.

This area is shown in figs. 3 and 4. It is fan-shaped in distribution, the stem of the fan commencing just above the posterior point of trisection of the fronto-parietal operculum, and the upper portion extending considerably over the border of the hemisphere, and in its hinder part involving and passing slightly beyond the sulcus cinguli on to the gyrus of this name.

On the external surface (fig. 3) the posterior edge of the fan in its middle third almost coincides with the bottom of the furrow of Rolando, the Betz-cells extending just posterior to the mid-line of the furrow in many sections.

The area is sharply defined throughout with the exception of three regions. The stem shades downwards to a point concurrently with a decrease in the size and number of the Betz-cells; and anteriorly

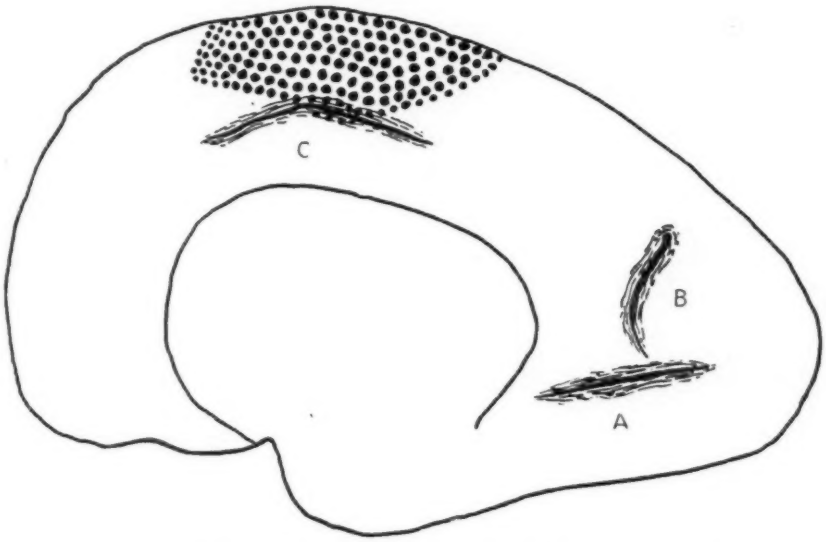


FIG. 4.—Two diameters. Inner surface of right hemisphere. The Betz-cell area is mapped out in dots. The small dots indicate where the area shades into the surrounding cortex, a sharp line of demarcation existing elsewhere. A, (permanent) stem of calcarine fissure; B, parieto-occipital (temporary) fissure; C, fissura cinguli.

and posteriorly at the upper angles of the fan, as is shown by the smaller dots on the diagram, the characteristic cortex undergoes some degree of shading into the cortex beyond. This is more evident anteriorly than posteriorly (fig. 4), and it is permissible to assume that this shading indicates that the evolution of the area is not yet complete at the sites where it occurs. The reasons for this interpretation will be given during the description of the visuo-sensory area.

Certain features of this somewhat peculiar Betz-cell area are worthy of remark. Its large size in relation to the hemisphere merits com-

parison with its very early appearance. Its position with regard to the furrow of Rolando is so characteristically human as to afford a useful illustration of the truth that in the complex of phylogenetic and ontogenetic factors which subserve the process of evolution, the latter from a very early period play a predominant part. Lastly, to trench for a moment on more purely histological details, the high evolution of this region as a well-defined cortical area, at a time when such adult guiding lines as the furrow of Rolando and the sulcus cinguli are merely indicated, is surely proof positive, even to a prejudiced observer, that, as one of us long ago suggested, lamination and histological differentiation precede fissuration. The latter must therefore be regarded as a probable—in many instances, perhaps, a merely possible—consequent on the former.

## V.—The Localization of the Visuo-sensory Area.

The limits of the left visuo-sensory area are indicated on fig. 5.

As has already been remarked, the stem of the calcarine fissure (A), which remains a permanent feature of the fissural system, is present, whereas the temporary parieto-occipital fissure (B) has almost disappeared. No indications are yet present of the pits which later form the body and the posterior extremity of the calcarine fissure.

The visuo-sensory area is pear-shaped, in many respects resembling the appearance of this area in the adult. At its anterior extremity, it commences on the lower lip of the stem of the calcarine fissure, and as it extends backwards it spreads so as to involve also the upper lip. Almost from its commencement it extends downwards well beyond the inferior lip of the stem of the calcarine fissure. Not, however, until just before it passes beyond the stem of the calcarine fissure into the unfissured cortex behind this, does it extend upwards beyond the line of the upper lip of the calcarine fissure. This area in many respects resembles in distribution the visuo-sensory area of a case of anophthalmos of the age of one month, which was published by one of us (J. S. B.) many years ago [1]. It thus produces belated evidence that the latter is not a freak of development, but actually represents the distribution and extent of the visuo-sensory area at some period of evolution which is slightly ahead of eighteen weeks of intra-uterine development, and which is probably the period at which in this particular case of anophthalmos evolution ceased.

The visuo-sensory area under description presents the following special features.

It is in a much earlier stage of development than is the Betz-cell area already described. Its existence as a cortical area is, in fact, determined, not by any special features of cyto-architecture beyond the preliminary cleavage of neuroblasts, but by its characteristic situation, extent and distribution.

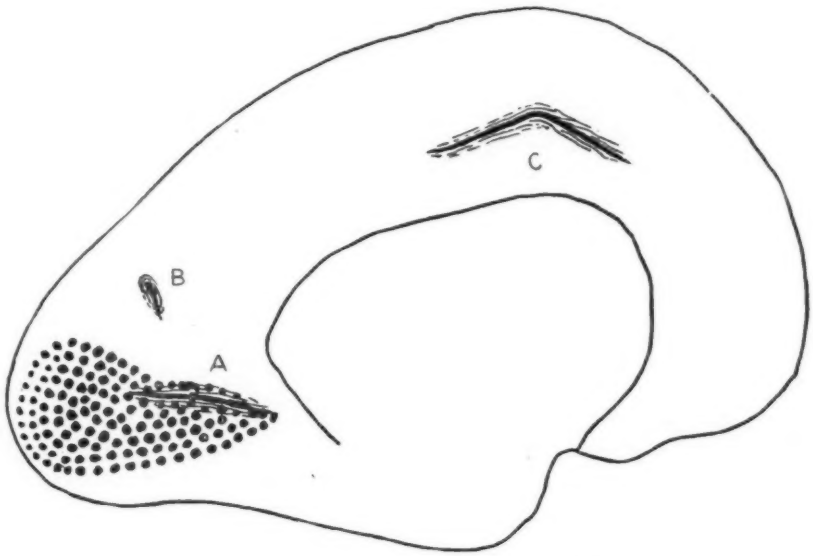


FIG. 5.—Two diameters. Inner surface of left hemisphere. The visuo-sensory area is mapped out in dots. Posteriorly, as is indicated by the smaller dots, it shades into the surrounding cortex. A, (permanent) stem of calcarine fissure; B, parieto-occipital (temporary) fissure; C, fissura cinguli.

In degree of development, and in actual depth of cortex, the part in relation to and below the stem of the calcarine fissure is by far the best part of the area. Posteriorly to the fissure, the cortex is much thinner, and towards the hinder limits of the area some degree of shading into the surrounding undifferentiated cortex occurs. It is, therefore, quite evident that development is proceeding from before backwards, as three grades of this exist, namely, the anterior good part in relation with the stem of the calcarine fissure, the middle thin part behind the fissure, and the posterior part which shades backwards. The fact that development has not yet occurred far, either histologically or from the point of view of distribution, may probably be correlated with the fact that the visuo-

sensory area, in relation to the hemisphere as a whole, is proportionally smaller than is the Betz-cell area.

As with the Betz-cell area, so in the case of the visuo-sensory area, it is clear that lamination and histological differentiation of the area precede fissuration, for in this case the area is determinable, although the body and posterior extremity of the calcarine fissure are not due to develop for a considerable time.

## VI.—The Cyto-architecture of the Cortex.

A description will now be attempted of the various types of lamination which we have been able to define in the cortex of the brain under investigation. The more definite of these will be illustrated by micro-photographs. With regard to the latter it is desirable to point out that, owing to the thinness of the cortex, and to the crowding of this with small cells, it has been necessary to enlarge the specimens to the unusual degree of 133 diameters. This has been done by means of a long extension apparatus, since the lenses at our disposal did not permit of any other method of displaying the whole of the cortex in each specimen. The results, though good for the method, are hence not as satisfactory us we could wish; and the subdivision of the microphotographs into laminæ is much less definite in the illustrations than is the lamination in the actual specimens.

(1) *The precentral (Betz-cell) cortex.*—The cortex of the Betz-cell area is composed of neuroblasts which as yet, apart from the Betz-cells, are embryonic and indifferent as regards structure.

Beneath the outer fibre-lamina (L.I), which approximately occupies one-seventh of the total depth, is the outer cell-lamina (L.II), arranged as irregularly-columnar rows of cells placed vertical to the external surface. No middle cell-lamina (L.III) is apparent, as is to be expected in an agranular region. The outer cell-lamina (L.II), also in depth occupying about one-seventh of the cortex, is separated from the inner cell-lamina (L.V) by the broad inner fibre-lamina (L.IV), which in its lower part contains the Betz-cells. The chief feature which distinguishes the inner fibre-lamina from the superjacent and subjacent cell-laminæ is the sparseness of the scattered and irregularly placed cells which it contains. This lamina is somewhat deeper than is the subjacent inner cell-lamina, occupying about three-sevenths of the total depth, whereas the latter occupies little more than two-sevenths of this. The Betz-cells thus lie less than two-thirds of the depth of the

cortex from the surface, whereas in the adult they lie at a depth of about three-quarters. In other words, in this fœtus these cells lie in a position which is intermediate between their respective positions in the cortices of the dog and the rhesus.

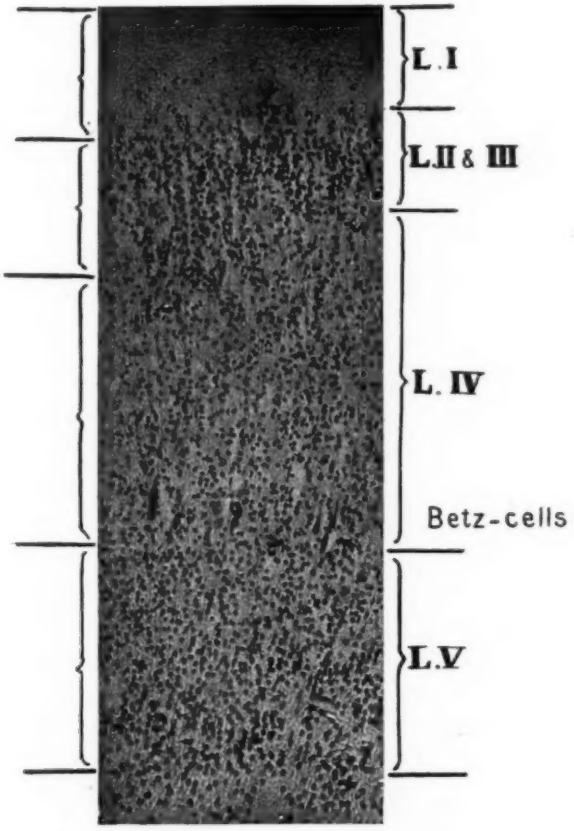


FIG. 6.—One hundred and thirty-three diameters. The precentral cortex. L.I, the outer fibre-lamina; L.II and L.III, the outer cell- or pyramidal-lamina, and the middle cell- or granule-lamina; L.IV, the inner fibre-lamina, which contains a layer of Betz-cells in its lower part; L.V, the inner cell- or polymorphic lamina.

As is illustrated in fig. 6, the Betz-cells lie in groups in every way similar to those seen in the adult cortex. They however differ somewhat in shape and size from adult cells. In sections stained by the

same method, an ordinary large adult Betz-cell measures on the average 30 $\mu$ by 50 $\mu$. The Betz-cells under description vary in length from 29 $\mu$ to 36 $\mu$, and are about 7 $\mu$ in width at the base. The nucleus, which is very constant in size, measures about 5·5 $\mu$ in diameter. Compared with adult cells, these cells are therefore relatively narrow and pyramid-shaped. As is well shown in the illustration (fig. 7), they are large and

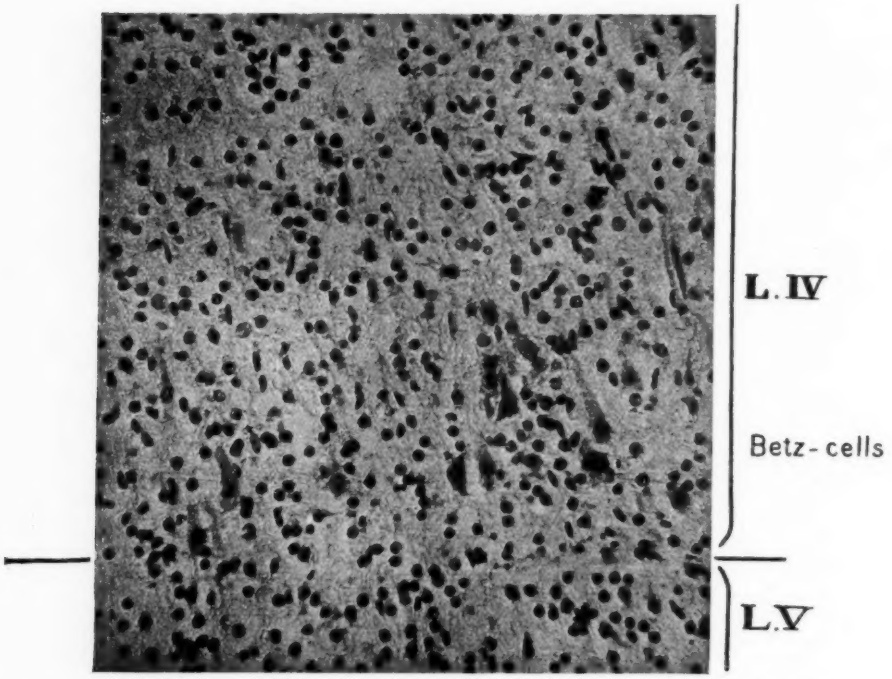


FIG. 7.—Three hundred and eighty diameters. The precentral cortex. L.IV, the lower part of the inner fibre-lamina, containing Betz-cells near its bottom; L.V, the upper part of the inner cell- or polymorphic lamina.

conspicuous objects, and are as readily visible in a well-stained section as are normal Betz-cells. Their topographical distribution is similar to that in the adult, the largest cells lying in the neighbourhood of the upper border of the hemisphere.

As has already been remarked, the Betz-cells extend backwards over the anterior lip and wall of the furrow of Rolando to the bottom of the fissure, and in several sections they may be seen extending back-

wards to just beyond this point. We have ourselves seen single Betz-cells extending to just beyond the bottom of the furrow of Rolando in more than one adult brain, and therefore regard the above relationship of the Betz-cells to the furrow of Rolando as within the normal limits. It is, however, only right to state that Campbell, in his monograph, remarks, "It is important to note that the cortex under consideration does not extend quite to the floor of the fissure" (of Rolando) "in any part." During the descent of the mammalian scale it is well known that the Betz-cell area reaches backwards to a decreasing extent. Whether our own or Campbell's views are correct with regard to the adult relationship of the area to the furrow of Rolando, it is nevertheless certain that the distribution in the fœtus under investigation is in this respect human rather than subhuman, which is the point we wish to emphasize.

(2) *The post-central cortex.*—In the immediate neighbourhood of the furrow of Rolando (posterior wall and posterior lip of the fissure), the whole depth of the cortex is thickly strewn with cells, so thickly in fact that the lamination is obscured. There is, however, a vertical columnar arrangement of the cells to be seen in the upper sixth or so of the total cell-depth, and the lower quarter or so of the total depth of cells tends to be separated from the rest as the inner cell-lamina. This region is extremely difficult to subdivide into laminæ, but we have satisfied ourselves that the lamination marked out in the illustration (fig. 8) is correct. According to this the outer fibre-lamina (L.I) occupies about one-sixth of the total depth, the outer cell-lamina (L.II) occupies a similar depth, the middle cell-lamina (L.III) occupies about one-third of the total depth, the inner-fibre-lamina (L.IV) occupies a a twelfth or less, and the inner cell-lamina (L.V) completes the cortex. Whether this interpretation of the lamination is correct or not, the marked preponderance of cells, compared with their relative sparsity in the pre-Rolandic cortex, is strongly suggestive of the probability that this cortex is concerned with the performance of sensory-projection functions. As the latter is *known* to be the case, it is likely that our interpretation of the lamination is correct, although in this particular case such interpretation must be regarded as an opinion rather than a certain observation.

More posteriorly the type of lamination alters and becomes more definite. Here the outer fibre-lamina (L.I) is of course evident. Below this the upper half of the remainder is occupied by the outer and middle cell-laminæ (L.II and L.III). The greater and more superficial part (L.II) tends to be columnar, and the lesser and deeper part tends

to be diffuse (L.III). The deeper part of the cortex is readily separated into the inner fibre-lamina (L. IV) with very few cells, and the deeper inner cell-lamina (L.V) with numerous cells.

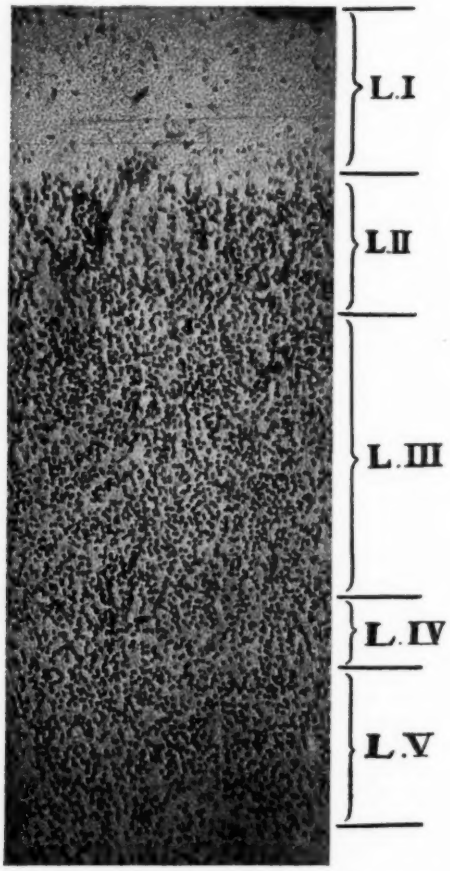


FIG. 8.—One hundred and thirty-three diameters. The post-central cortex. L.I, the outer fibre-lamina; L.II, the outer cell- or pyramidal lamina; L.III, the middle-cell, or granule-lamina; L.IV, the inner fibre-lamina; L.V, the inner cell- or polymorphic lamina.

It is hardly necessary to point out to a reader familiar with the diagrams of Campbell and of Brodmann, especially the latter, that the pre- and post-central cortices of this fœtus of eighteen weeks present

appearances which, immaturity being allowed for, are identical with those of the normal adult. The precentral Betz-cell area is efferent, psychomotor or cerebral-associative-motor, and corresponds with "4," if not also "6," of Brodmann, and with the "precentral," if not also the "intermediate pre-central" of Campbell. The post-central cortex on the other hand corresponds with "3," "1" and "2" of Brodmann and shades backwards into "5," "7" and "40," and, in the case of the diagram of Campbell, with the "post-central" and "intermediate post-central," shading backwards into the "parietal" of this observer. The attempted compromise made by one of us [3] between the views of Brodmann and Campbell on the one hand and the "bodily sensibility projection area" of Flechsig on the other thus fails when the necessary information is available. It was regarded as possible that during early fœtal development the general sensory projection area might not occupy the identical site in which it lies in the adult, in which case Flechsig's inclusion of the precentral gyrus, &c., in this area might be true, since his researches were conducted by the method of myelogenesis. In view, however, of the evidence which we have adduced with regard to the cyto-architecture of the precentral and post-central cortex in a fœtus of eighteen weeks, it is certain that even at this early period of development the normal adult structure is already laid down. It is necessary therefore to conclude that Flechsig's areas "1," "1a," "1b," and "6" do not correctly represent the "bodily sensibility projection area" in the fœtus. Area "1" and the posterior part of area "1b" together must be regarded functionally as earlier and later afferent-projection regions, and area "1a," and the anterior part of area "1b," together with area "6," must similarly be regarded functionally as earlier and later efferent-projection regions. This *must* be the case, since the afferent and efferent cortical regions are well differentiated with regard to their future functions at a period long prior to that at which myelogenesis commences. We do not, however, wish to impugn the correctness of the observations of such a master in research as Flechsig, and therefore suggest a further and more probable explanation of his results.

In the brain under description, the pre- and post-central regions are far and away the best developed parts of the cortex. It seems reasonable to us to assume that this remarkable development of the cortical part of the great sensori-motor machine at such an early period of evolution bears a definite relationship, from the aspect of ontogenesis, to the already stable condition of the lower reflex mechanisms. The

latter truth is of course evidenced by the reflex movements of the fœtus *in utero*, which about this period of development not only are active, but also are readily felt by the mother. Since the sensory or afferent fibres to the cortex in all probability develop before the motor or

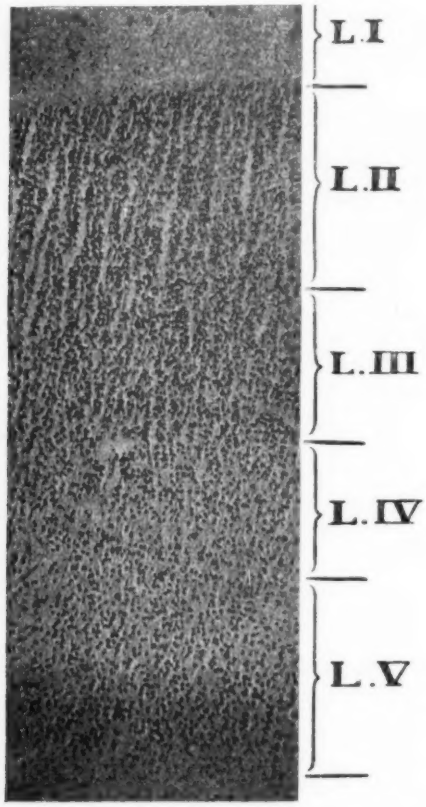


FIG. 9.—One hundred and forty-four diameters. The anterior, and best developed, part of the visuo-sensory area, on the lower lip of the calcarine fissure (*cf.* fig. 10). L.I, the outer fibre-lamina; L.II, the outer cell- or pyramidal lamina; L.III, the middle cell- or granule-lamina; L.IV, the inner fibre-lamina; L.V, the inner cell- or polymorphic lamina.

efferent fibres from the cortex, it is certainly *possible* that the former may be distinguishable from the latter by the study of their myelogenesis, but it is extremely improbable. In fact, since the efferent cortical fibres originate from the Betz-cells, and have a considerable

distance to travel, whereas the afferent cortical fibres do not travel uninterruptedly, it is extremely unlikely that at any period of fœtal development it is possible to make an absolute distinction between such afferent and efferent fibres. It is thus possible to accept the results of Flechsig as correct, without at the same time accepting the conclusions which he draws from them, and especially is this the case since the

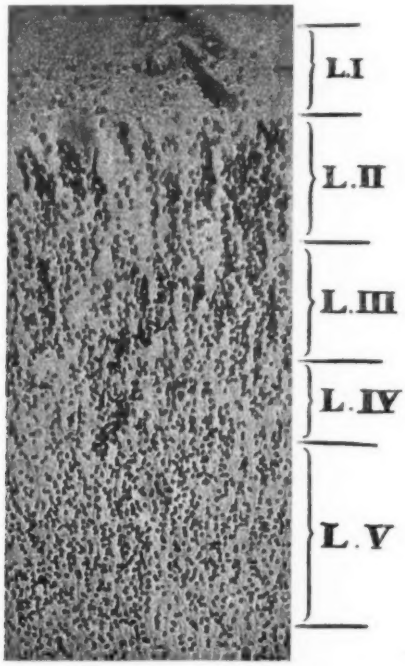


FIG. 10.—One hundred and thirty-three diameters. The posterior, and less well-developed part of the visuo-sensory area (*cf.* fig. 9). L.I, the outer fibre-lamina; L.II, the outer cell- or pyramidal lamina; L.III, the middle cell- or granule-lamina; L.IV, the inner fibre-lamina; L.V, the inner cell- or polymorphic lamina.

cortex, from the neuronic aspect, is so well developed at a period long prior to the commencement of myelogenesis. We would remark, in order to escape the criticism that the above observations are purely theoretical, that they are inserted with the sole object of defending a renowned investigator, whose researches have served as the origin, if not as the basis, of the fruitful work of the past twenty years.

(3) *The cortex of the visuo-sensory area.*—Throughout this area, which is in a very early stage of development, the distinguishing feature is a cleavage of the neuroblasts owing to the development of the inner fibre-lamina, which cleavage allows of the mapping out of an area possessing, as has already been indicated, all the characteristic features of extent and distribution of the adult visuo-sensory area. As has been stated, the anterior part of the area, namely, that related to the existing stem of the calcarine fissure, is the best developed, the posterior portion being, however, exactly similar in type, though thinner and in an earlier stage of evolution. The anterior and posterior portions are respectively illustrated in figs. 9 and 10. The outer fibre-lamina (L.I) is obvious, and the inner fibre-lamina (L.IV) is in the anterior part (fig. 9) equally definite, though not quite so obvious in the posterior portion of the area (fig. 10).

Between these laminæ is a mass of neurones, which together represent the outer and middle cell-laminæ (L.II and L.III). The former part consists of cells which are arranged in vertical columnar bundles, which shade downwards into the diffusely arranged cells of the middle cell-lamina (L.III). Below the inner fibre-lamina (L.IV) is the inner cell-lamina (L.V), which is composed of an aggregation of smaller cells lying closely packed. The cells of this lamina are smaller and less embryonic in structure than are the rest of the cells of this part of the cortex, in accordance with the general law under which the cortex laminates and develops from within outwards.

The lamination of the posterior part of the visuo-sensory area is identical, with the exception of the fact that the cortex is thinner and the separation into laminæ is not quite so obvious.

Surrounding the visuo-sensory area is a type of cortex which we take to represent the visuo-psychic, since the features presented by it allow of this deduction.

Its lamination is as follows: The outer fibre-lamina (L.I) is as usual. The outer cell-lamina (L.II) is deeper than the corresponding lamina of the visuo-sensory area, but is similarly composed of cells lying in vertical columnar bundles. The middle cell-lamina (L.III) is much narrower than the corresponding lamina in the visuo-sensory area and is difficult to define, as it practically constitutes the lowermost part of the lamina above it in this region. The inner fibre-lamina (L.IV) is shallower and much less evident than the corresponding lamina of the visuo-sensory area, but is quite visible. It contains many fewer cells than the latter. Finally, the inner cell-lamina (L.V) is much

shallower than the corresponding lamina of the visuo-sensory area and its constituent cells are on the whole slightly larger and more embryonic.

(4) *The cortex of the gyrus cinguli.*—The portion of the cortex of this gyrus, which is illustrated in fig. 11, is that below the anterior extremity of the Betz-cell area. In the brain under description this region is at the anterior part of the gyrus cinguli, and in an adult brain the homologous region would probably be about the middle of the gyrus.

Between the Betz-cell area and the cortex of the cingulate gyrus lies an intermediate type of cortex which will first be described. The outer fibre-lamina (L.I) shows nothing unusual. Below this, for about one-third of the rest of the depth of the cortex, and representing the outer and middle cell-laminæ (L.II and L.III), lie vertical columns of embryonic cells. The inner fibre-lamina (L.IV), with relatively very few contained cells, lies below this mass of cells, and below it again is the inner cell-lamina (L.V), which is fairly broad and very definite, and consists of a mass of well-developed cells. This type of cortex extends from the Betz-cell area down over the upper lip of the cingulate fissure, across the bottom of this, and up the lower lip. It is here replaced by the cortex of the cingulate gyrus, which contains fewer elements and is of very different structure, and obviously older, as is shown by the more developed and less embryonic appearance of its constituent cells.

The structure of this cortex (fig. 11) is as follows: The outer fibre-lamina (L.I) is of the usual appearance and occupies about one-eighth of the depth of the cortex. Below this lies the conjoined and inseparable outer and middle cell-laminæ (L.II and L.III). This conjoined lamina is very narrow, occupying but one-eighth of the depth of the cortex. The cells are arranged in vertical columns, and are very embryonic in appearance and possess large nuclei. Below this comes the broad inner fibre-lamina (L.IV), which occupies no less than three-eighths of the depth of the cortex. It contains scattered cells of pyramidal type which are better developed than those above them and possess rather smaller nuclei. The remaining three-eighths of the cortex consist of the inner cell-lamina (L.V). This lamina is very well developed and contains numerous cells which are smaller and older than those above them and possess much smaller nuclei. In brief, the characteristic features of this type of cortex are the very high evolution of the inner cell-lamina (L.V), the good development of the

inner fibre-lamina (L.IV), and the very poor evolution of the middle and outer cell-laminæ (L.II and L.III).

(5) *The cortex of the anterior frontal region.*—The chief feature of the anterior frontal cortex is its extreme thinness. At the same time, however, there are definite indications of a cleavage of the neuroblasts slightly below their middle (fig. 12).

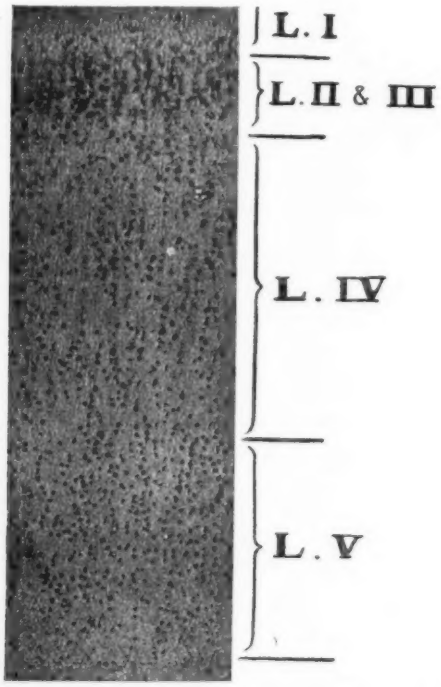


FIG. 11.—One hundred and thirty-three diameters. The cortex of the gyrus cinguli below the anterior part of the Betz-cell area. L.I, the outer fibre-lamina: L.II, the outer cell- or pyramidal lamina; L.III, the middle cell- or granule-lamina: L.IV, the inner fibre-lamina; L.V, the inner cell- or polymorphic lamina.

The arrangement of the neuroblasts is irregularly mixed rather than vertically columnar, in the upper part, and the very common pairing or quadrupling of the neuroblasts, &c., indicates proliferation of probably all the elements, whether capillaries, neuroglia or neuroblasts. In some cases rows of as many as six elements suggest the columnar arrange-

ment of cortex of later development. This appearance, though by no means entirely peculiar to the anterior frontal region of this case, is much more marked and definite here than elsewhere. The cortex thus consists roughly of four portions, of which the first and third are rather less deep than the second and fourth. The first is the outer fibre-lamina (L.I). The second is the precursor of the outer and middle cell-laminæ (L.II and L.III). The third represents the inner fibre-lamina (L.IV), and the fourth is the inner cell-lamina (L.V).

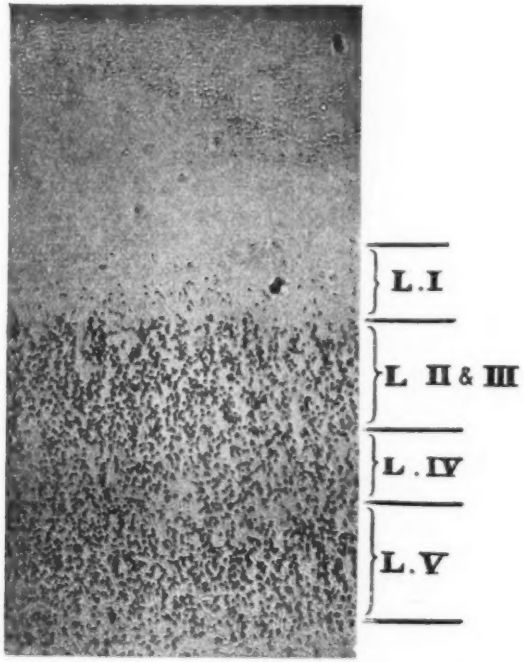


FIG. 12.—One hundred and thirty-three diameters. The very embryonic anterior frontal cortex. L.I, the outer fibre-lamina; L.II, the outer cell- or pyramidal lamina: L.III, the middle cell- or granule-lamina; L.IV, the inner fibre-lamina; L.V, the inner cell- or polymorphic lamina.

The characteristic feature of this type of cortex is the fact that all the neuroblasts are equally embryonic, the inner cell-lamina (L.V) being as under-developed as the middle and outer cell-laminæ (L.III and L.II). The anterior frontal cortex thus markedly contrasts with

the cortex of the cingulate gyrus, an obviously, and well-known, earlier type, in which L.V is very well developed, L.IV is well developed and L.III and L.II are very poorly evolved.

## VII.—Summary.

By the histological examination of the cerebrum of a fœtus of eighteen weeks we have arrived at the following results (amongst others) :—

(1) Considerable progress has already occurred with regard to the specialization of cortical areas and the differentiation of neuroblasts.

(2) The Betz-cells are well developed, and the relatively very large Betz-cell area can be accurately mapped out.

(3) The visuo-sensory area can be defined with accuracy. In the case of this area, however, specialization of the cortex and differentiation of the neuroblasts are both less advanced.

(4) The pre- and post-central cortices and the visuo-sensory area already possess the adult relationships to the Rolandic and calcarine fissures respectively.

(5) The pre- and post-central cortices are remarkably well evolved in comparison with the rest of the cortex.

(6) The cingulate cortex is of poor quality but is relatively well advanced in development.

(7) The anterior frontal cortex, on the other hand, is throughout its depth extremely embryonic in structure.

(8) There is very definite evidence that, in the complex of phylogenetic and ontogenetic factors which subserve the process of evolution, the latter from a very early period play a predominant part.

(9) The cleavage of the developing neuroblasts of the cortex into upper and lower portions, which enclose between them the precursor of the inner line of Baillarger, takes place at a much earlier period than we have hitherto supposed. This is clear, since this line (L.IV) is indicated in the rudimentary anterior frontal cortex, and since the Betz-cells which are contained in it in the pre-central region are so well developed.

### REFERENCES.

[1] Bolton, J. S. "The Exact Histological Localization of the Visual Area of the Human Cerebral Cortex," *Phil. Trans.*, 1900, B, vol. cxciii, pp. 165-222.

[2] *Idem.* "The Histological Basis of Amentia and Dementia," *Archives of Neurol.*, 1908, vol. ii, pp. 424-620b.

[3] *Idem.* "A Contribution to the Localization of Cerebral Function, based on the Clinico-Pathological Study of Mental Disease," *Brain*, 1910-1911, vol. xxxiii, pp. 26-148.

[4] BRODMANN, K. "Beiträge zur histologischen Lokalization der Grosshirnrinde," *Journ. f. Psychol. u. Neurol.*, 1902-7, but especially Mitteilung VI, "Die Cortexgliederung des Menschen," 1907, Bd. Heft 6.

[5] *Idem.* "Vergleichende Lokalizationslehre der Grosshirnrinde," Leipzig, 1909.

[6] CAMPBELL, A. W. "Histological Studies on the Localization of Cerebral Function," Cambridge, 1905.

[7] CUNNINGHAM, D. J. "Contribution to the Surface Anatomy of the Cerebral Hemispheres," 1892. Roy. Irish Acad. "Cunningham Memoirs," 1892, vol. vii, pp. 1-358.

[8] FLECHSIG, P. "Gehirn und Seele," Leipzig, 1896.

[9] MOTT, F. W. "The Progressive Evolution of the Structure and Functions of the Visual Cortex in Mammalia," *Archives of Neurol.*, 1907, vol. iii.

[10] MOTT, F. W., and KELLEY. "Complete Survey of the Cell Lamination of the Cerebral Cortex of the Lemur," *Proc. Roy. Soc.*, 1908, Ser. B, vol. lxxx, p. 488.

[11] MOTT, F. W., SCHUSTER, E., and HALLIBURTON, W. D. "Cortical Lamination and Localization in the Brain of the Marmoset," *Proc. Roy. Soc.*, 1910, Ser. B, vol. lxxxii, p. 124.

[12] MOTT, F. W., SCHUSTER, E., and SHERRINGTON, C. S. "Motor Localization in the Brain of the Gibbon, correlated with a Histological Examination," *Proc. Roy. Soc.*, 1912, Ser. B, vol. lxxxiv, p. 67.

[13] SYMINGTON, J. "Quain's Elements of Anatomy," 1908, vol. iii, part i, p. 289.

[14] WATSON, G. A. "The Mammalian Cerebral Cortex, with Special Reference to its Comparative Histology. I—Order, Insectivora," *Archives of Neurol.*, 1907, vol. iii, p. 49.

# A CASE OF GENERALIZED STREPTOTRICHOSIS WITH EXTENSIVE LESIONS IN THE CENTRAL NERVOUS SYSTEM.

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THE case recorded here derives its interest mainly from the lesions found in the brain and meninges, streptotrichial infection in this region being an occurrence of some rarity. Howard [11], writing in 1903, finds only eighteen cases in the literature. A case reported by Delépine [7] in 1889 is not included in Howard's list, which gives details of all the eighteen cases, and from which many of the following particulars have been obtained, and since 1903 two further cases have been described, one by McDonald [13] in 1904, and one by Beevor and Buzzard [4] in 1903.

If we include the case under consideration the total number of recorded cases is twenty-two.

Considering these in a little more detail we find that in five cases the lesions in the central nervous system were described as primary, that is, no further lesions of a streptotrichial nature were discovered, while in the remaining seventeen cases lesions of a similar nature were found elsewhere in the body.

The lesions found in the central nervous system consisted of cerebral abscesses, almost always multiple, and meningitis.

In thirteen cases cerebral abscesses were present without meningitis.

In three cases the meninges were affected without abscess formation.

In six cases both abscesses and meningitis were present.

The abscess formation observed in these cases shows considerable similarity of character, and need not be further noticed here. With regard to those cases in which the meninges were affected, however, the lesions seem to have differed considerably.

Thus in a case recorded by Almquist [2], on the true nature of which Howard throws considerable doubt, the lesion found was a cerebrospinal meningitis.

Dolore [8] records a case in which a cerebrospinal pachymeningitis of streptotrichial origin was the only lesion present.

In Beevor and Buzzard's [4] case a basal leptomeningitis was present, and this was the type of meningeal lesion found in the present case, and in the remaining cases described, excluding a case described by Ponfick [14] in which the lesion commenced extracranially and perforated the skull, producing a localized meningitis and abscess formation.

Batten [3], writing on meningitis, says: "Streptothrix infection of the meninges is a rare condition. It is most commonly found as an extension from a focus in the skull or soft parts of the face and throat, but some cases of primary infection have been recorded. Sometimes true metastatic foci have been found in the meninges secondary to infection in other parts of the body."

On examining the nine cases mentioned above, however, we find that in two cases only has infection of the cranial bones been noted, namely, one case reported by Ponfick [14] and alluded to above, and the case described by Beevor and Buzzard [4] in which caries of the sphenoid was found.

In Almquist's [2] doubtful case the meningeal lesion was considered as primary, while in the remaining six cases the meningitis was part of a more general infection.

Thus in Dolore's [8] case the original lesion was one affecting the neck and face.

In Chiari's [6] two cases the brain lesions were secondary to a streptotrichial bronchiectasis. In Eppinger's [9] case the bronchial and supraclavicular glands were primarily affected. In the case described by Keller [12] an abscess in the thoracic wall was the only other lesion present, while in the case under consideration the liver and lungs were the seat of streptotrichosis.

Indeed, if we extend the list to include the remaining thirteen cases, in which the meninges were unaffected, we find no further mention of disease of the cranial bones, so that metastatic infection would seem to be the rule in these cases.

In this connexion certain facts observed in the above cases are of some interest. Thus, dealing with the microscopical features of the organisms present in the twenty-two cases, in seven cases clubs and rosettes are mentioned as being absent or very rare. In only one case, that described by Bollinger [5], were typical colonies with club formation definitely stated to be present, while in the case under con-

sideration very definite club formation was present in the colonies in the central nervous system.

Delépine [7], in describing the lesions present in the case recorded by him says: "In a few vessels bacilli were also found, but it was not possible to determine whether they were adventitious products or not. They looked, however, not unlike segments of the more typical filaments found in the abscesses, and were probably early forms of the organism." No such appearances could be observed in the present case.

In the majority of cases in which an accurate description of the organism is given it is described as consisting of a few branching thread forms, sometimes in twisted masses, usually showing little beading and with a marked absence of club formation.

Dealing briefly with the relative frequency of streptotrichosis of the central nervous system as compared with a similar condition in other parts of the body the following figures taken from an article by Acland [1] may be given. Duvan, writing in 1902, and quoted by Acland, gives the following details of 257 cases:—

| | | | |
|---|---|---|---|
| Face and neck .. .. .. | 70 | Central nervous system .. | 19 |
| Thorax .. .. .. .. | 65 | Generative organs .. .. | 19 |
| Liver.. .. .. .. .. | 40 | Œsophagus .. .. .. | 7 |

In the same article Acland gives the following table showing the situations of the lesions in 109 cases of streptotrichosis occurring in the United Kingdom between the years 1884 and 1906:—

| | | | |
|---|---|---|---|
| Abdomen (including liver) .. | 68 | Brain and spinal cord .. .. | 5 |
| Face, neck, tongue, &c. ... .. | 50 | Acute general .. .. .. | 9 |
| Chest.. .. .. .. .. | 29 | | |

The case under immediate consideration will now be described, and finally a few special points in connection with it considered.

While in the hospital the patient was under the care of Dr. Hawkins, and later of Mr. Makins, and it is through their kindness that I am enabled to record it here.

The patient, a man, aged 45, by trade a horsekeeper, was admitted to St. Thomas's Hospital on January 31, 1911, with a large tender swelling in the lower part of the abdomen, and gave the following history.

On January 7 he first noticed a feeling of tenderness over the lower part of the abdomen. No swelling was then present. A few days afterwards a small hard swelling appeared, which gradually increased in size. The tenderness and pain continued, and were increased after a heavy meal or on coughing.

The patient stated that he had never vomited, but that he had always suffered from a slight tendency to constipation.

Inquiries as to his family history yielded no information of importance. The only facts of interest in his past history were as follows:

He contracted syphilis at sixteen years of age. The chancre was followed by a rash, but no further lesions developed.

From 1886 to 1903 patient served in the Army, and from 1886 to 1889 was stationed in India, where he had repeated malarial attacks.

He had lost "about a stone" in weight during the six months preceding admission.

The following was the state on admission:

The heart, lungs, and nervous system were all found to be normal. The urine showed nothing abnormal.

A tumour could be seen and felt, occupying the hypogastric region, and extending slightly into the umbilical and left iliac regions.

The percussion note over the tumour was impaired; the tumour possessed well-defined edges; it did not pulsate; no fluctuation could be made out, and the skin was nowhere adherent over it. The swelling increased in size, and a week after admission the skin over its most prominent part became adherent, and fluctuation was felt.

On the eighth day the patient, who had been running an irregular temperature, varying between normal and 102° F., had a rigor, and the temperature rose to 103·5° F.

The following day an incision was made into the swelling, and about half a pint of foul-smelling pus of a yellow colour was removed, and the cavity drained.

The pus was examined in the Clinical Laboratory, and returned as sterile.

About the same time the patient's serum was tested for the Wassermann reaction with a positive result.

The wound continued to discharge for seven weeks, during which time the patient's condition showed little change, and then, on April 1, he had another rigor, the temperature then returning to the slightly irregular course, varying between 97·5° F. and 100° F., which it had followed since the first operation.

The blood was examined for malarial parasites without result. A count of the white-cells revealed a leucocytosis of 16,600 per c.mm.

On April 24 an exploratory laparotomy was performed. The appendix was found behind the cæcum. It was about 5 in. long, and showed signs of old disease, but there was no obvious connexion between it and the abscess in the anterior abdominal wall. It was removed.

This operation was followed by a temporary improvement in the condition of the patient, but on April 12 he had another rigor, and the temperature continued of a pyæmic type until June 6, accompanied by frequent rigors.

On May 15 the percussion note over the base of the left lung was noted as impaired, and a few crepitations were audible in this region. These signs gradually extended, and eventually involved the greater part of both lungs.

A frequent cough developed with expectoration, and an examination of the sputum revealed the presence of elastic fibres.

A blood culture taken about the same time was found to be sterile.

From June 6 to June 23 the temperature remained at a lower level, never rising above 101° F.; but on June 17 patient had a series of fits beginning in each case with clonic movements of the left arm and leg, which then became generalized, and were succeeded by a period of rigidity. The patient became noticeably cyanosed during these attacks, and on several occasions bit his tongue. Unconsciousness usually lasted for ten to fifteen minutes, and after regaining consciousness the patient usually slept for several hours.

These attacks were repeated on June 18 and 19.

On July 3 paralysis was first noticed affecting the left arm and leg, and more marked in the former.

Both knee-jerks were slightly exaggerated.

The right planter reflex was extensor, the left indefinite. On the same date the patient was noted to be suffering from a left hæmianopia.

Two days later incontinence of urine and fæces developed, the paresis became more profound, and the patient died on July 8. Frequent rigors occurred from June 23 to the time of death.

## Post-mortem Examination.

The *post-mortem* examination revealed the following conditions. Scars indicating the incision into the abscess and the laparotomy were present. The lower end of the former scar still showed a red granulomatous area.

On opening the abdominal cavity the intestines immediately adjacent to the laparotomy scar were found to be adherent to the abdominal wall, but the peritoneal cavity appeared otherwise healthy.

*The liver.*—Throughout the upper part of the right lobe were scattered 12 to 20 small white nodules varying in size from about ½ in. in diameter down to the size of small shot. The smaller of these were of comparatively firm consistence, but the larger were breaking down in the centre, and on pressure yellowish pus exuded. No granules were present.

*The lungs* were riddled throughout with small shotty nodules having about the same range of size as those seen in the liver, but the smaller considerably predominating. All the larger and most of the smaller nodules yielded on pressure pus of the same type as that found in the liver, and here again no granules could be seen.

*The brain.*—The base was covered with thick yellowish pus over an area extending from the under surface of the cerebellum posteriorly to the optic chiasma anteriorly. The pus did not reach to the lower

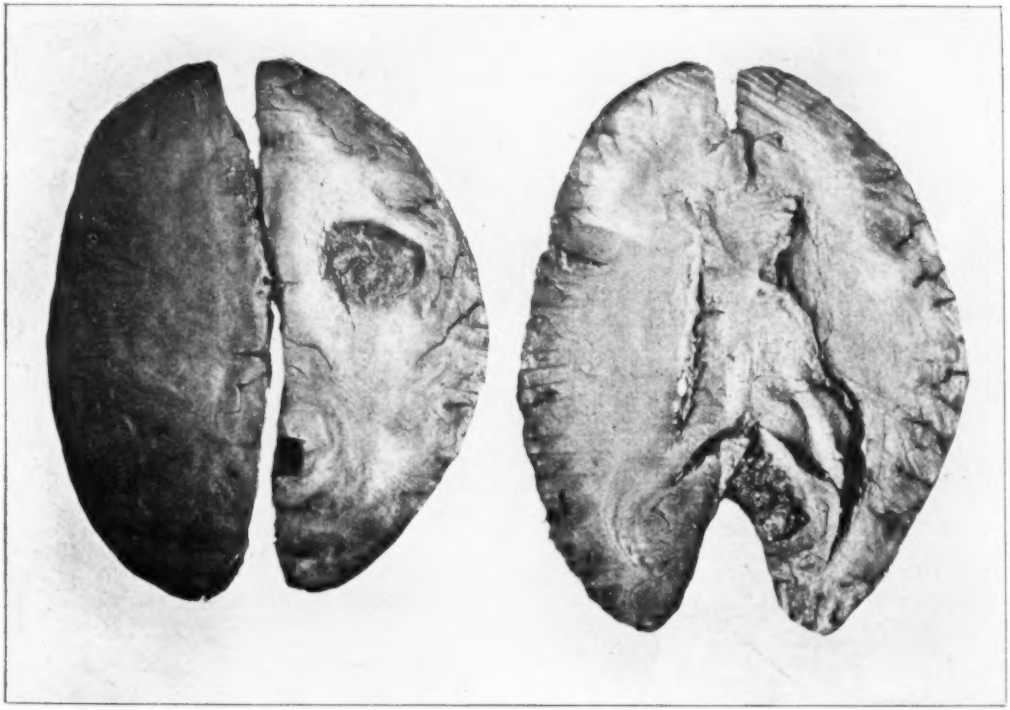

FIG. 1.—Showing a large single abscess lying beneath the right ascending frontal convolution. A small portion of brain-tissue has been removed from the right occipital lobe for microscopical examination.

FIG. 2.—Showing a smaller more irregular abscess situated in the right occipital lobe just anterior to the calcarine fissure.

part of the medulla, or upper part of the cervical cord; the remainder of the cord was not removed.

The obvious deformity of the brain revealed the presence of extensive suppuration within its substance; one large abscess indeed burst during examination, but only a minute quantity of pus escaped.

The brain was then hardened for twenty-one days.

*The spleen* was large, dark red in colour, and of soft consistence.

*The appendix* had been amputated.

*The kidneys, heart, intestines, and remaining organs* showed no naked-eye changes.

After hardening, the brain was further examined, with the result that the following areas of suppuration were discovered (figs. 1 and 2).

(1) A large, single, irregular abscess-cavity lying deep to the upper half of the right ascending frontal convolution, right Rolandic fissure and right ascending parietal convolution and extending forwards beneath the hinder part of the superior and middle frontal convolutions.

In its lower part it lay altogether in the white matter, in its upper part the cortex itself was excavated, and in one place, in the upper half of the right ascending frontal convolution, only a very thin shell of cortex covered the cavity (figs. 3 and 4).

(2) A smaller, more irregular and somewhat loculated abscess situated in the right occipital lobe just anterior to the calcarine fissure, the cortex in the neighbourhood of which was extensively invaded.

(3) A very large, multilocular abscess, consisting of two large pockets and many smaller ones affecting the left frontal lobe, which was very largely destroyed. This cavity was much distended with pus, and the right frontal lobe was markedly displaced and compressed as a result of the enlargement of the opposite lobe. Scattered around this large abscess cavity were many small foci of suppuration, not directly connected with the main cavity.

The pus in all these abscesses was of the same type as that observed in the liver and lungs, and though granular débris was present no bodies of the "mustard seed" type could be observed. The walls of the cavities were ragged and showed no attempt at encapsulation. On opening the ventricles they were found full of a slightly turbid fluid, but sections taken from the various parts of their walls showed no evidence of extension of the disease in this direction.

Microscopical sections were prepared from the liver, lungs, cerebral tissue and meninges; tissue being chosen in each case, which, to the naked eye, appeared to be in the earlier stages of the disease—i.e., the

FIGS. 3 and 4.—Showing a large multilocular abscess situated in the left frontal lobe. The two main cavities communicated through the aperture seen in the right-hand figure. Note the extreme deformity of the whole right hemisphere, especially the frontal lobe.

sections passed through the smaller foci where breaking down of tissue and pus-formation was least advanced. The sections were stained by Gram's method in each case.

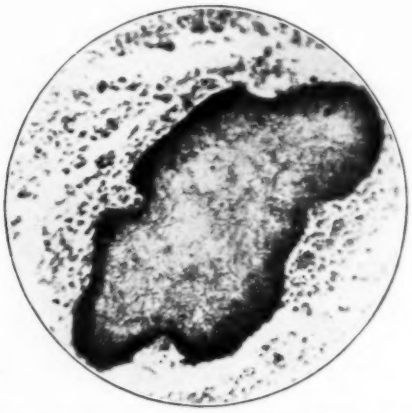

FIG. 5.—A streptothrix colony from a section obtained from the liver. Note the complete absence of radial clubs.

FIG. 6.—A streptothrix colony from a section obtained from the wall of a cerebral abscess. Note the well-marked radial clubs.

Typical colonies of a streptothrix were obtained in a certain number of sections from all the lesions.

A remarkable difference, well shown in the accompanying micro-photographs, was observed between the colonies in the brain and those elsewhere. (Figs. 5 and 6.)

Whereas the colonies in the liver, for instance, showed the appearances usually found in human streptotrichosis, with little or no attempt at radial club formation, the colonies in the cerebral lesions showed the most marked radial club-formation, resembling that seen in the bovine disease, save that in no case did these clubs retain the stain by Gram's method.

The threads themselves showed marked beading in almost every case, and many coccus-like bodies were present in the majority of colonies.

The cellular reaction was largely of the mononuclear type, with a considerable admixture of polymorphonuclear cells in most cases.

An attempt was made to cultivate the organism from the pus from the liver abscess, but only a mixed staphylococcic growth resulted. The cultural characteristics could not, therefore, be made out, and it is impossible to relegate the organism to any special class.

One of the main points of interest in this case is, perhaps, the question of the original site of infection.

The appendix was found at the operation placed retro-cæcally, and was slightly thickened and fibrosed. The thickening was slight only, and there was no sign of any caseative or suppurative process, that is, the organ showed none of the lesions which are usually associated with streptothrix infection in this region. But Foulerton [10] says, "The tendency to natural cure must also be remembered as a possible explanation of cases in which streptotrichial lesions occur only in parts which would seem not liable to become the seat of a primary infection from without; thus in a single focus of infection in the liver it is always possible that there may have been a primary infection of some part of the intestinal canal, the initial lesion having meanwhile become healed."

It is thus possible that the condition of the appendix represented an old, healed streptotrichial lesion.

The next question is whether the abdominal abscess was of the same nature.

There are two facts which point in the opposite direction: (1) In the course of the examination of the pus from this abscess which was sterile on culture, the possibility of actinomycosis was thought of, and the organism searched for with negative results; (2) although streptotrichial lesions may heal under certain conditions, this is true, in most cases, only of slight lesions; and it is certainly exceptional for a streptotrichial lesion of the extent of the abscess noted to heal as completely as was the case in this patient.

The obvious alternative is that the abscess was in reality a breaking-down gumma, and additional weight is given to this view by the history of syphilitic infection and the presence of a positive Wassermann reaction.

Whatever the seat of the primary infection, there seems no doubt in this case that the final distribution occurred viâ the blood-stream, and was of the nature of a true pyæmia.

The reason of the marked radial club-formation is by no means obvious.

The cerebral lesions were certainly terminal in character, and it is improbable that they were of long standing. A clue is perhaps afforded by some further remarks of Foulerton's [10]; after pointing out that infection seems usually to be spread in the body by short rod segments which then branch and not by the spore forms, where further development would occur in the typical radial manner, he says, "In some circumstances, as when a suppurating cavity in the lung is in communication with the air, spore forms may be present in abundance, and being conveyed elsewhere may doubtless originate fresh foci of infection."

In this case the clinical findings make it almost certain that the pulmonary lesions preceded the cerebral.

## Conclusions.

The case here recorded presented extensive lesions in the central nervous system, consisting of a basal lepto-meningitis, and multiple cerebral abscesses.

These lesions were proved to be streptotrichial in nature by the demonstration of colonies of the organism in microscopical sections.

There was no disease of the cranial bones or of the soft tissues of the head or neck, but extensive streptotrichial lesions were found elsewhere in the body. It is therefore clear that the cerebral lesions resulted in this case from an infection of a pyæmic type, and not as the result of extension from neighbouring parts, and a study of the literature would suggest that infection by the blood-stream is the rule in cases of streptotrichosis in this situation.

The colonies of the streptothrix found in the cerebral lesions showed certain marked differences from those found in the liver and lungs, and these differences may, perhaps, be accounted for by the different forms in which the infection may have been carried, in the one case as

true spore-forms from the pre-existing pulmonary lesions, in the other as short filaments, which would appear to be the more common method.

## REFERENCES.


[1] ACLAND. Article on Actinomycosis in Clifford Allbutt's "System of Medicine," Second Edition, 1906, vol. ii, part i, p. 324.

[2] ALMQUIST. *Zeitschr. f. Hygiene u. Infectionskrank.*, 1890, vol. viii, p. 189.

[3] BATTEN. Article on Meningitis in Clifford Allbutt's "System of Medicine," Second Edition, 1910, vol. viii, p. 165.

[4] BEEVOR and BUZZARD. *Trans. Path. Soc. Lond.*, 1903, vol. liv, p. 320,

[5] BOLLINGER. *Münch. med. Wochenschr.*, 1887, vol. xxxiv, p. 789.

[6] CHIARI. *Zeitschr. f. Heilk.*, 1900, xxi, Abth. Path. Anat., p. 351.

[7] DELÉPINE. *Trans. Path. Soc. Lond.*, 1889, vol. xl, p. 420.

[8] DOLORE. *Gaz. Hebdom. de Méd. et Chir.*, 1896, N.S., vol. i, p. 496.

[9] EPPINGER. *Bietrag. zur Path. Anat. u. Allg. Path.*, 1891, vol. ix, p. 287.

[10] FOULERTON. Article on Pathology of Streptothrix Infections in Clifford Allbutt's "System of Medicine," Second Edition, 1906, vol. ii, part i, p. 302.

[11] HOWARD. *Trans. Assoc. Amer. Phys.*, 1903, vol. xviii, p. 427; also in *Journ. Med. Research*, 1903, vol. lx, p. 301.

[12] KELLER. *Brit. Med. Journ.*, 1890, vol. i, p. 709.

[13] MCDONALD. *Scott. Med. and Surg. Journ.*, 1904, vol. xiv, p. 305.

[14] PONFICK. "Actinomykose des Menschen," Berlin, 1882.

# PROGRESSIVE SPINAL MUSCULAR ATROPHY OF INFANTS (WERDNIG-HOFFMANN TYPE).

BY F. E. BATTEN, M.D.
AND
GORDON HOLMES, M.D.

THE following case was under our care in the Out-patient and the In-patient Departments of the National Hospital, and was exhibited at the Clinical Section of the Royal Society of Medicine on February 10, 1911, as a case of the Werdnig-Hoffmann type of the progressive spinal muscular atrophy of infants.

Some differences of opinion existed at first as to the diagnosis of the case, and it was originally suggested that the condition resembled that described by Oppenheim under the name "myatonia congenita." But though there was considerable loss of tone in the muscles, the marked paresis of the proximal muscles as compared with the distal, and the paralysis of the intercostal muscles pointed to a myelopathic rather than a myopathic disease.

## CLINICAL HISTORY.

The patient was the second of two children. The elder, a boy, died at the age of eight months of broncho-pneumonia; the parents described him as loose in his limbs and more or less similarly affected. No other instance of nervous disease was known in the family.

The patient was first seen in the Out-patient Department of the National Hospital in June, 1910, when she was 1 year 2 months old. She was born at the seventh month and had been delicate during the first four months of life, but she moved and kicked about as other children till she was about 6 months old. Then she seemed fat and healthy and was able to sit up, but was not encouraged to do so. At this age she was vaccinated and she cut her first tooth, but from this time onwards her parents noticed her becoming weaker and more helpless. At seven months she was able to say a few words. Between nine and twelve months she lost almost all power in her limbs and became unable to sit up, or to hold her head erect when it was unsupported.

When she was first seen she was a well nourished and fairly developed

child; all her limbs were weak, especially at their proximal joints, and if she were placed in a sitting posture her back bent under her weight and her head hung backwards or to either side as drawn by gravity. Her limbs were flabby and toneless, but the atrophy of the muscles was obscured by a thick covering of subcutaneous fat. All the deep reflexes were absent. The movements of the eyes, face and tongue seemed unaffected, and the child was bright and intelligent. During the first few months that she was under observation she appeared to her mother to become a little stronger, but in October, 1910, at the age of eighteen months she was reported to be weaker, and then slight muscular contractures in the legs were noticed for the first time.

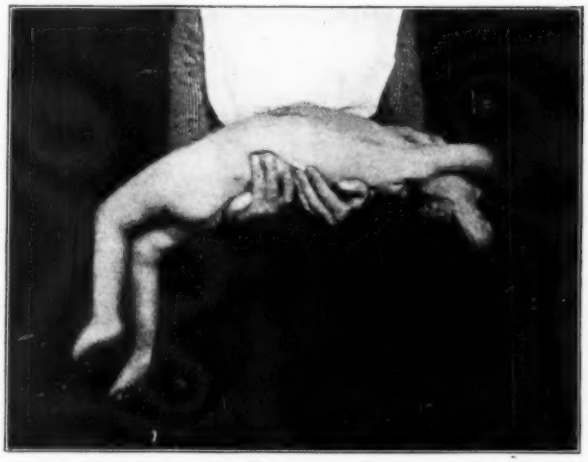

FIG. 1.—Photograph of child lying in nurse's arms showing her "limp" condition and her inability to raise her head or flex her legs.

She was admitted to hospital in January, 1911, at the age of one year and nine months. She was a bright and intelligent child and seemed to take an interest in all around her. She could talk, but it was difficult to understand what she said. She was easily upset and then cried in a normal manner, but evidently with very little breath, each few sobs being followed by an interval in which she made a few deep inspirations with considerable effort. The palpebral fissures were narrow and this gave the child the appearance which had been called "mongoloid," but apart from this there was nothing to suggest that she was a mongoloid idiot. The forehead had a central prominence over the frontal suture, but otherwise the head was normally shaped and measured 19½ inches in circumference. There was no sign of rickets; the incisors, canines and first molar teeth were present.

The movements of the eyes, jaws, tongue and lips were quite normal, and the child swallowed without difficulty. She could also see and hear well, and obeyed commands as far as her muscular power permitted. Her optic discs were normal.

She could not raise her head from the pillow or even turn it from side to side. When placed in the sitting position the head fell backwards, or forwards, or to either side, the neck muscles being almost powerless. Her back also became bent, as there was no power in the trunk muscles either to fix or straighten the spine (figs. 1 and 2). When placed flat in

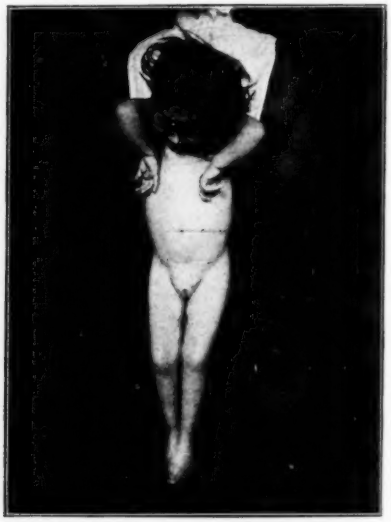

FIG. 2.—Photograph of child held up by a nurse; the head falls forward and the arms tend to "come away" from the trunk.

the bed, however, the spine became perfectly straight. The other trunk muscles were equally weak, with the exception of the diaphragm, which contracted vigorously. Her chest was long and narrow, and on each inspiration the intercostal spaces sank in, respiration being almost wholly diaphragmatic. The abdominal muscles though very weak were not completely paralysed.

The arms as a rule lay flexed at the sides of the chest, with the forearms pronated. She could make small movements with the fingers and grasp objects feebly, and could just flex and pronate the elbows, but not supinate the forearms. There was no power of movement however at the shoulder-joints. The lower limbs were almost powerless; practically no movement was possible at the hips or knees, but she had slight power of flexion and

extension of the ankles and toes. The hamstrings were slightly contractured, so that the knees could not be fully extended.

The limbs were thin and their muscles much wasted, but this wasting was, to a considerable extent, obscured by subcutaneous fat. The muscles were also toneless, but the feet could not be brought over the shoulders nor the arms crossed behind her back, positions which are possible when there is marked hypotonia in a child.

Electrical examination showed complete loss of response to faradism in all the paralysed muscles, but the muscles of the hands responded fairly well. The child bore strong currents without evincing any signs of pain. In short, the child had an almost complete flaccid paralysis of all the muscles of the neck, trunk and limbs, the muscles of the face, eyes, and the diaphragm alone remaining normal.

Sensation to ordinary stimuli appeared to be unimpaired all over the body. The knee-jerks, ankle-jerks and the other deep reflexes were absent, but the sphincter functions were unaffected.

The child was removed from hospital in April, 1911, and died at home in the following January at the age of 2 years and 9 months.

The *post-mortem examination* was performed in the child's home forty-eight hours after death. There was then no rigor mortis present. The body appeared well nourished and so well covered with fat that the muscular wasting was scarcely apparent. When the skin was incised a thick layer of pale adipose tissue was found, and the muscles of the limbs and of the pelvic- and shoulder-girdles were so small and pale that it was, in certain instances, difficult to recognize them. Further, when they were cut across they were found to be soft and flabby, and the pallor was evidently due to the amount of fat they contained. This flabbiness and pallor of the muscles were more marked in the proximal segments of the limbs than in the distal. The rectus abdominis seemed to be less affected than most of the limb muscles, but the erector spinæ were extremely wasted and pale. The diaphragm was the only muscle which, in naked-eye appearance, approximated to the normal. Portions of a large number of muscles were taken for microscopical examination; they were fixed in Zenker's fluid, and embedded and cut in celloidin.

The larger nerve-trunks appeared unaffected to the naked eye; it could not be said they were smaller than normal. The brain and spinal cord also appeared normal, though the ventral roots of all segments of the cord were remarkably small and slender.

## Microscopical Examination.

*Nervous system.*—The brain, spinal cord and several peripheral nerves were examined by Marchi's and by Weigert-Pal's methods, and in sections stained by hæmatoxylin and van Gieson's picro-fuchsin; several sections of the spinal cord were also stained by Nissl's method.

The Marchi method shows no evidence of either recent or old degeneration

in any part of the central or of the peripheral nervous system. The medullated fibres of the medulla oblongata and spinal cord stained well by the Weigert-Pal method, and there is no evidence of degeneration of any of the longer tracts. On the other hand, the staining of the medullated fibres in the grey matter is defective, and the medullated meshwork in the ventral horns is thinner than normal. The ventral roots in both their intra- and extra-medullary courses are small and poorly stained, while the dorsal roots appear normal and stain well. The only definite change that is revealed by this method in the peripheral nerves is an apparent loss of fibres in some of the bundles, while a certain proportion of the fibres that remain are small and poorly stained.

Sections of the spinal cord stained by van Gieson's method show no inflammation or interstitial change, but the most striking feature apparent in sections of all regions is a paucity of cells in the ventral horns, and the small size of those cells which remain. In sections stained by Nissl's method the same remarkable deficiency of ventral horn-cells is even more striking. The small cells show no marked deviation from the normal; they appear like normal cells in miniature. The nuclei and nucleoli are situated centrally, and the chromophilic substance stains well.

All groups of ventral horn-cells are severely affected, but the postero-lateral group in the cervical region is relatively best preserved. This deficiency of cells was confirmed by an enumeration of all those visible in a series of sections 10 $\mu$ thick. In fifteen sections from the third lumbar segment, for instance, there was an average of only eight cells in the right ventral horn and 7·7 in the left, while in these fifteen sections only seven large cells were counted, the others being all small. For the same segment of the normal cord, Bruce gives the average number of large cells as forty-seven, and nine small cells per section. Figs. 8, 9, 10 and 11, which are photographs and drawings of sections from the same segments of the cervical regions of the affected and of a normal cord, illustrate very well the deficiency in number and the diminution in size of the ventral horn-cells. The control is taken from the cord of a child, aged 10 months, and therefore considerably younger than the patient. Another normal cord from a child, aged 5, was also compared with that of our patient, and, although there is but little difference in the size and number of cells at these two ages, the comparison with the cord of the younger seems fairer, and this has been consequently reproduced.

The cells of the rest of the grey matter of the spinal cord appear normal in size and number; Clarke's column and the intermedio-lateral cells of the lateral horn seem large and extremely well developed in contrast with the cells of the ventral horns.

*Muscles.*—The muscles which were removed from the body and have been examined were the trapezius, the pectoralis major, the rectus femoris, the biceps femoris, the rectus abdominis, the erector spinæ, the flexors of the fingers and the diaphragm.

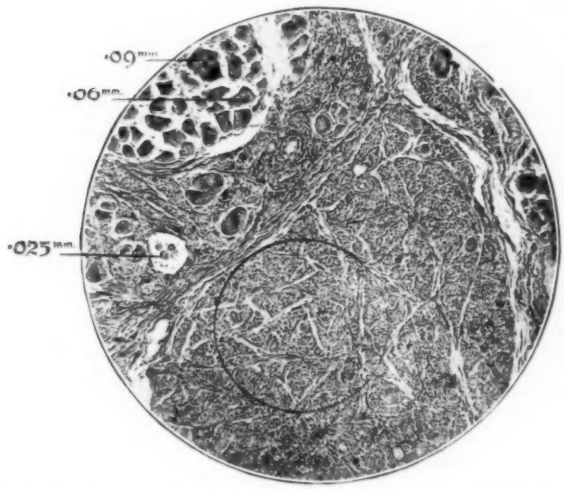


FIG. 3.—Transverse section of pectoralis major muscle, showing general structure of the muscle. A bundle of normal muscle-fibres is seen in the section; these measure from 0·04—0·9 mm. in diameter. Scattered about the section are a few isolated fibres of normal size; but the majority of fibres have undergone extreme atrophy and measure 0·01 mm. and less. A muscle-spindle containing four muscle-fibres is seen, the intra-fusal fibres measure 0·025 mm., which is normal for these fibres. Magnification about 50 diameters.
The small circle indicates the area represented in the more highly magnified fig. 4.

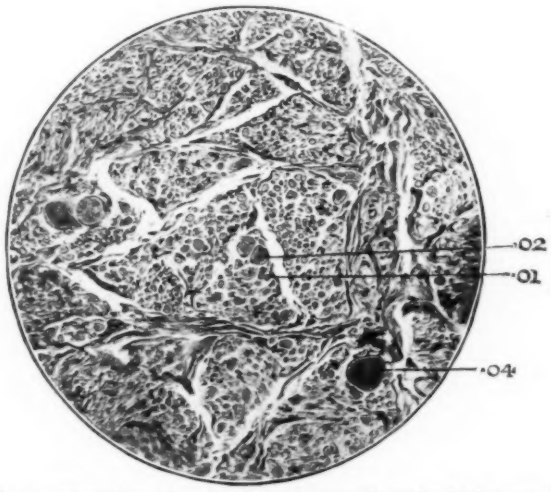


FIG. 4.—Transverse section of pectoralis major muscle under higher magnification. It shows a few comparatively large fibres about 0·04 mm., but most of the fibres measure 0·01 mm., and some as little as 0·003. Magnification about 150 diameters.
There is little or no increase of the connective tissue between the individual fibres.

All these muscles have been cut in transverse and longitudinal sections, and stained by the van Gieson method.

The diaphragm alone of all the muscles examined shows no pathological change.

The changes in the affected muscles are strikingly similar, though they vary somewhat in the degree to which they affect the different muscles. All the muscles show a large number of atrophied or undeveloped muscle-fibres, with a few bundles of well-developed fibres. There is generally an increase in the amount of interstitial fat, and the connective tissue between the bundles is increased, although there is but little or no increase between the individual fibres. The latter feature stands out in rather striking contrast to the condition found in a myopathic muscle.

FIG. 5.—Transverse section of biceps femoris showing several large isolated fibres, some of which are surrounded by a number of atrophic fibres. There are numerous bands of connective tissue between the various muscle bundles. Magnification about 150 diameters.

A description of a section of the pectoralis major (fig. 3) will serve as an example of the changes present in all the muscles. In this muscle, bundles of normal muscle-fibres having a polygonal shape can be seen measuring ·06 to ·09 mm. in diameter (fig. 3). In close proximity to such normal bundles are bundles containing fibres of very small size, some measuring as little as ·0025 mm. Between these minute and atrophied fibres and the normal fibres all varieties of sizes are seen. Many of the small fibres are round or oval in outline, and not of the normal polygonal shape in cross-section. In some bundles in which almost all fibres are of small size a few large isolated fibres of a round or oval shape are present measuring ·04 mm. (fig. 4). The nuclei

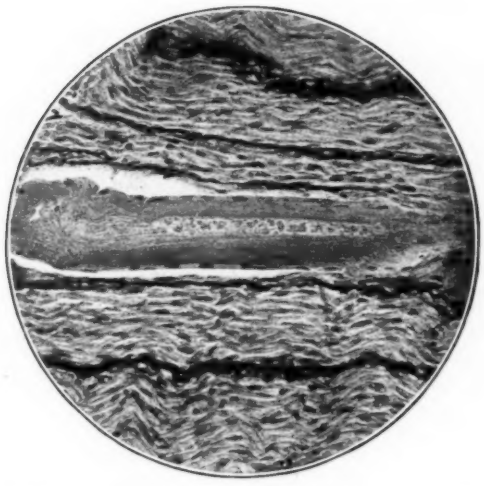

FIG. 6.—Longitudinal section of anterior tibial muscle showing degeneration of the centre of a large muscle-fibre. The neighbouring fibres have undergone extreme atrophy.

FIG. 7.—Section of rectus femoris muscle showing large fibres splitting into numerous fine fibres. The transverse striation of these small muscle-fibres is well preserved.

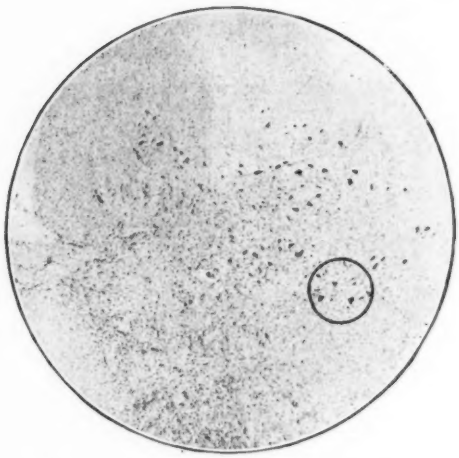

FIG. 8.—Photographs of the anterior horn of the cervical region of the spinal cord of a normal child, aged 10 months, to compare with the fig. 9. The section has been taken from the same segment in the cervical region, and has been similarly stained and photographed under the same magnification. The circle indicates the position of the cells seen under higher magnification in fig. 10.

FIG. 9.—Anterior horn of the cervical region of the spinal cord showing the marked diminution in the number of the cells and the small size of those which still remain. The circle indicates the position of the cells seen under higher magnification in fig. 11.

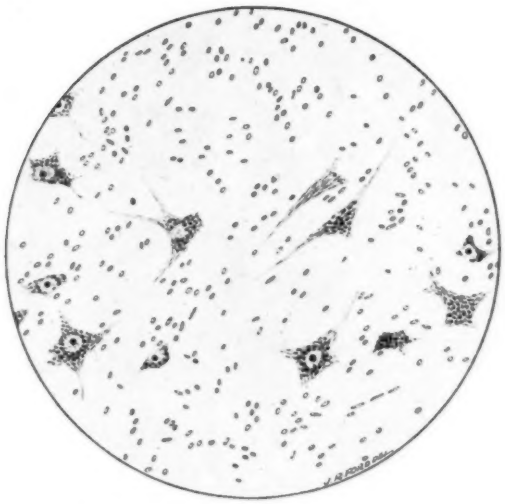

FIG. 10.—Normal cells of the anterior horn under high power (child aged 10 months).

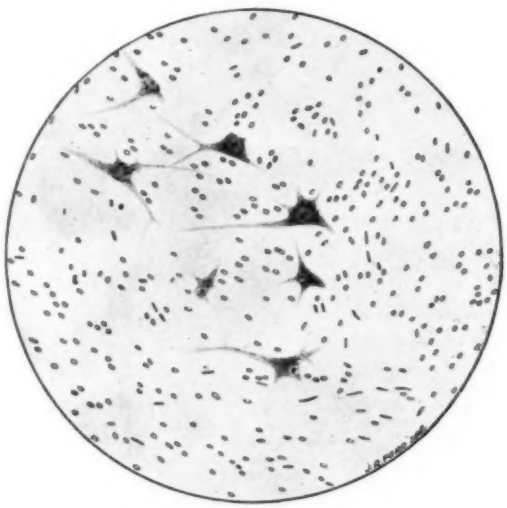

FIG. 11.—Cells of anterior horn under same magnification, showing their relatively small size and comparatively normal appearance.

Figs. 10 and 11 have been reproduced from drawings made from photographs taken under the same magnification.

(Drawings have been used in the place of photographs because of the impossibility of obtaining clear photographs of all the cells in the field.)

of the muscle-sheaths are in most places normal; but in others are grouped together, and form a dark band surrounding certain muscle-fibres.

The connective tissues between the bundles is relatively increased owing to the smallness of the muscle-fibres (fig. 5).

Most of the fibres, even those which are extremely small, show normal transverse striation (fig. 7).

Some few fibres show central degeneration (fig. 6), and some sections show a splitting up of a large fibre into numerous fine fibres (fig. 7). There is an increase of the interstitial fat in some muscles; but it is not a marked feature. Numerous muscle-spindles can be seen, and their intra-fusal fibres appear of the normal size, viz., about ·02 mm. in diameter (fig. 3).

*To summarize*, it may be said that the majority of the muscle-fibres present the appearance of a simple atrophy, with but little, and often no, increase of connective tissue, or of nuclei between them. Large and abnormally thick bands of fibrous tissue, and an excess of fat are, however, present in all the affected muscles. It seems possible that many of the small muscle-fibres may never have developed, as they show very little of such degenerative changes as are met with in conditions of progressive muscular atrophy in the adult. The presence of abnormally large fibres of cylindrical outline, and the occurrence of central degenerative changes, and of fission of some of the large fibres is, however, evidence that at least some of the fibres have undergone retrogressive changes similar to those which occur in both primary myopathic affections, and in the spinal muscular atrophies.

*Commentary.*—The clinical diagnosis of this case presented some difficulties. The marked loss of tone in the muscles, together with their weakness, suggested at first that the case was one of myatonia congenita. The onset of the weakness during the first nine months of life, and its progressive nature, however, indicated that the condition was similar to that described by Werdnig and by Hoffmann in young children under the title of "Progressive Spinal Muscular Atrophy of Infants." In support of the view that the condition was due to a spinal atrophy attention should be called to the facts: (1) That the intercostal and abdominal muscles were weak and paralysed; (2) that the paralysis of all the more proximately situated muscles was relatively greater than of the distal muscles, and (3) that the loss of tone—hypotonia—was not so great in relation to the paralysis as that which is seen in typical cases of myatonia congenita. Neither the absence of the deep reflexes nor the electrical reactions could aid in the differential diagnosis.

On the pathological side the evidence is strongly in favour of regarding the condition as primarily myelopathic. The loss and atrophy

of the motor-cells of the ventral horns is very striking, and although similar changes have been described in a few cases of myopathy it has never been so severe, and in most cases no such atrophy of the spinal motor-cells is present. A similar diminution in the number and in the size of the cells has been found in the condition described by Oppenheim as myatonia congenita (Baudouin, Collier and Holmes), but it has not been nearly so severe as that which we found in this case.

It is, however, not altogether easy to confirm the view that in our case the disease is a primary myelopathic affection due to a degenerative process affecting the cells of the ventral horns, for no evidence of this degeneration in actual progress can be obtained either by the Marchi or by the Nissl method; though the latter method shows chromatolytic changes in a few cells, yet the essential feature is the *smallness* and normal appearance of such cells as are present. Even the muscle-changes cannot decide the question definitely, as it is now generally recognized that the histological differences between the primary and the secondary muscular atrophies are not so sharp and distinct as was at one time believed. Many of the changes which we have described in the muscle-fibres resemble closely those of the primary myopathies—smallness and atrophy of most of the fibres, increase in size and hypertrophy of others, central degeneration and fission of some of the hypertrophied fibres—and if we attempt to draw a distinction it must be in the relatively small amount of connective tissue that is found between the individual fibres, and in the absence or rarity of free muscle-nuclei, as compared with that which exists in dystrophic muscles. On the other hand, such features might be expected to occur if a dystrophy commenced at an exceptionally early age, when the development of the muscle-fibres is not completed or so advanced as at the age at which the disease usually sets in. It may be pointed out that the same relatively slight fibrosis of the affected muscles and rarity of free muscle-nuclei has been found in myatonia congenita, a disease which also sets in very early in life.

The whole question of the pathology of these cases of Werdnig-Hoffmann paralysis has been recently discussed by Batten in "Brain," 1911, and the cases recorded in the literature to that date are there given.

REFERENCES.

BATTEN. *Brain*, 1911, vol. xxxiii, p. 433.
BAUDOUIN. *La Sem. Méd.*, 1907, t. xxvii, p. 241.
COLLIER and HOLMES. *Brain*, 1909, vol. xxxii, p. 269.

# PROGRESSIVE SPINAL MUSCULAR ATROPHY OF YOUNG CHILDREN — WERDNIG-HOFFMANN TYPE. REPORT OF A CASE, WITH PATHOLOGICAL EXAMINATION.

BY LEONARD PARSONS, M.D., M.R.C.P.

AND

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THE Werdnig-Hoffmann type of progressive muscular atrophy of young children is a disease of extreme rarity. The original cases were described by Werdnig [6] in 1891, and Hoffmann [2] in 1894, and until the year 1898 there were clinical records of eight cases only with a pathological investigation in five of them. In a recent paper Batten [1] has analysed the recorded cases since that date. There have been five other pathological examinations, one of them being on one of the cases whose clinical particulars were described before 1898. Of cases without a pathological examination, Batten admits four only as true examples of the disease. In the course of the same paper he gives details of three cases with pathological examination, and also of two other examples of the disease which came under his notice, but where he was unable to carry out any *post-mortem* investigation. This brings the total number of well-authenticated recorded instances of the disease to twenty-one.

This disease attacks children, who in nearly all cases are healthy at birth, and it not infrequently affects more than one member of a family. Muscular weakness begins at the age of a few weeks or months, and commences in the muscles of the back and pelvic and shoulder-girdles, gradually spreading from there to the distal extremities of the limbs. The intercostal muscles and those of the abdominal wall are often atrophied. The cases go progressively downhill for weeks, months, or years. The age at which death occurs has varied from a few weeks (Batten) to six years (Werdnig, Thomson and Bruce [5]), and the fatal termination is not infrequently due to bronchopneumonia. *Post-mortem*, the constant pathological change is an atrophy of the anterior horn cells.

*Case.*—C. P., a boy, aged 3, was the fifth child of a family of six children, all of whom were born at full term, and three of whom died in infancy from "chest and fits." The sixth child, aged 18 months, can walk well. There were no miscarriages. Until 10 months old the patient was a "normal" child; he then had an attack of bronchitis, after which wasting became apparent. At a year he could move his legs quite well, also his arms at the elbow, but was unable to lift the arms above the shoulder. In the legs wasting was first observed in the upper part of the thigh. He was never able to sit up alone, although when propped up he was able to maintain that position for some time. He has been able to roll himself over, but has never been able to pull himself along the ground, to crawl, or to stand. For the twelve months before admission to hospital he has been unable to hold his head erect, although well able to do so before; this loss of power has been quite gradual, and even up to the date of his admission into hospital he was able on occasions to "roll his head" up. During this time he has also developed a deformity of the chest. Since the first attack of bronchitis he has had frequent similar attacks. For two years his voice has been getting weaker, although improving a little, with improvement in the chest condition. At the time he came to the Out-patient Department of the Children's Hospital, Birmingham, he was said to be putting on weight, and to be stronger than he had been for some time previously. In May, 1911, he was admitted.

On admission he was noticed to be a very intelligent boy, who talked quite well. He was markedly wasted, weighing 19 lb. He lay comfortably on his back in bed, and could be freely moved about without pain; he was unable to raise himself into a sitting position, but when propped up he could maintain that position for a little time. He was also unable to hold his head erect, and as a result his head flopped about, first on one shoulder and then on the other.

The ocular nerves appeared normal, the pupils were active and equal. There was no paralysis of the facial muscles, tongue, or palate, and swallowing was normal.

His arms were thin, flaccid, and assumed a position of pronation. The muscles of the shoulder-girdle were most affected, being nearly completely paralysed. Supination was impossible, and there was well-marked wrist-drop. He could hold objects in his hand, and with great difficulty convey a small spoon to his mouth. All movements of the fingers could be carried out, but in a very weak manner. The small muscles of the hand did not appear to be wasted. The fingers were long and thin, and their extremities were bulbous. The hands generally assumed the following position: Wrist-drop, flexion at the metacarpophalangeal joints, and extension of the interphalangeal joints of the second to fifth digit; the metacarpal of the thumb slightly opposed to the palm with hyper-extension at both metacarpo- and inter-phalangeal joints. In grasping objects the first and second digits were usually employed, and these with a slow, seizing action, not unlike the way in which a lobster uses his large claws in seizing objects. This curious "athetoid" movement and the

amount of overaction accompanying it has been pointed out by Batten. The lower limbs were very thin, the wasting being most apparent above the knee. Both limbs were adducted, the left to a greater degree than the right, internally rotated, and slightly flexed at both hip- and knee-joints. The right foot was in the position of a talipes equino-varus, and the left foot lay on its inner side with the sole everted. The legs could not be extended fully at the knee- or hip-joints and the adductors showed a considerable amount of contracture; apart from this the flaccidity of the limbs was very marked, and passive movements could be freely performed. Of voluntary movements he was only able to flex and extend his toes, and to flex and extend the ankle. These movements were rather weak, especially that of extension of the toes, and therefore the ankle was kept in an extended position. The feet did not appear to be wasted.

Both hands and feet showed a considerable degree of hypotonia, but the most striking feature was the flaccid paralysis of arms and legs. The abdominal muscles were very atrophic, the abdomen being ballooned, and many fæcal masses could be felt through the abdominal wall. Respiration was entirely diaphragmatic, and the intercostal, together with the abdominal, muscles appeared to be completely paralysed. The thorax showed a very well-marked deformity of the "Trichterbrust" variety. The back muscles were weak and wasted. When the child was propped up, there was a well-marked lateral curvature in the lower dorsal and lumbar regions, having its convexity towards the left.

The knee-, ankle-, and arm-jerks, and the abdominal reflexes were all absent. Plantar reflexes were indefinite in type, and the organic reflexes were all normal. No alteration in sensation was found. Electrical examination showed a marked diminution of excitability and a slight reaction of degeneration. Lumbar puncture gave a clear fluid which showed a few lymphocytes, but hardly more than normal.

He remained in hospital until his death from bronchopneumonia in October, 1911. During this time the amount of paralysis did not appear to increase in the arms, and sometimes he appeared to have more strength in his neck muscles than at others. Paralysis in the lower limbs rather increased, and a day or so before his death the only movements possible were very feeble extension and flexion of the toes. Movement at the ankle-joint appeared to be impossible, and a condition of slight pes cavus had developed.

*Autopsy.*—This was performed twenty-four hours after death. The limbs retained the positions described above, they were covered with a fair amount of subcutaneous fat which made the muscular wasting even more marked than had been expected. Of the muscles examined the erector spinæ, glutei, latissimus dorsi, rhomboids and trapezius (particularly the lower half) were all small and atrophied. The sternomastoid and the pectoralis major were also very pale and atrophic, but not to the same degree throughout, the sternal part of the sternomastoid and the upper part of the pectoralis major being less affected than the other parts of the muscles. The pectoralis minor was also very wasted, and the intercostal muscles together with those of the abdominal wall

had almost completely disappeared; the few fibres which remained were very pale. The deltoid was pale and wasted to an extreme degree. The biceps and coracobrachialis were very wasted, but still contained a fair amount of apparently healthy fibres. The psoas and iliacus muscles, on the other hand, were extremely pale and atrophic. The diaphragm in contrast to the other muscles was of a good colour, and did not show any atrophy to the naked eye. All these changes appeared to be present in the same degree on both sides of the body.

There was very extensive bilateral bronchopneumonia. None of the other viscera showed any abnormality except that the intestines appeared to be thin walled.

The brain and cord showed no changes to the naked eye, but the anterior nerve-roots were smaller than normal.

*Microscopical examination.*—The muscles examined microscopically were the biceps, psoas and diaphragm. These were embedded in celloidin, and examined by Van Gieson's and Marchi methods. Paraffin sections of the intestine stained by hæmatoxylin and Van Gieson were also examined.

The biceps and psoas by Van Gieson's method show marked changes. (*See* figs. 1, 2, 3 and 4.) There is a considerable increase in the amount of fibrous tissue, which is in parts distinctly more cellular than usual; in places it forms dense bands separating the various muscle-bundles. The muscle-fibres show many variations, and these are not localized to any one particular part of the section, but seem to be distributed more or less through the whole muscle, so that bundles of apparently normal fibres are seen in close proximity with those showing very marked changes. The more normal fibres occupy a somewhat larger proportion of the muscle than the altered ones. The normal fibres seem to have rather more nuclei than the normal, and a few show central nuclei. Some of the fibres are much larger than normal, and have lost their polygonal outline, becoming rounded; others, although larger than normal, retain their polygonal outline. By far the greater proportion of the altered fibres are, however, smaller than the normal, some being extremely small and on the point of complete atrophy. These small fibres in cross section measure ·01 mm. and less, and show an enormous increase in the number of nuclei, so that parts of the section appear to be swarming with nuclei. On cross-section at first sight these nuclei rather appear to belong to fibroblastic cells. Some of them are, since fine fibrous tissue can be traced in between some of these fibres; but longitudinal section of the muscle shows that nearly all these nuclei belong to minute muscle-fibres, many of which exhibit very well-marked striation. These minute fibres seem to be formed by the splitting of larger fibres, and at the point of cleavage proliferation of the nuclei occurs. Many of these fine fibres seem to pass imperceptibly into fibrous tissue, and in cross-section some of them are seen embedded in fairly dense fibrous tissue.

Striation is on the whole well preserved. Some fibres seem to have lost their striation in whole or part, but on the other hand many of the small fibres retain their striation until their complete disappearance.

FIG. 1.—Cross section of biceps (× 80 diams.), stained with hæmatoxylin and Van Gieson's method. In the upper right quadrant are normal fibres. The majority of fibres are of the atrophic variety. Several muscle spindles are present and there is much fibrosis. The area enclosed by the ring forms fig. 2.

FIG. 2.—Higher magnification (× 250 diams.) of the part of fig. 1, enclosed by the ring, showing the characters of the atrophic muscle-fibres and of the fibrous tissue. Close to the centre is a normal muscle spindle. The atrophic fibres measure ·01 mm. and less in cross-section, and the fibres in the muscle spindle ·025 mm. and ·02 mm.

FIG. 3.—Cross-section of psoas (× 80 diams.) stained with hæmatoxylin and Van Gieson's method, showing fibrosis and close proximity of atrophic and more normal muscle-fibres. The area enclosed by ring forms fig. 4.

FIG. 4.—Higher magnification (× 250 diams.) of part of fig. 3 enclosed by the ring, showing variations in size of the atrophic fibres and the great increase in the number of nuclei.

Muscle-spindles show a normal structure; they are very well seen, and in the biceps particularly they are present in good numbers. They show no change even when situated in the middle of muscle-bundles of fine muscle-fibres (*see* figs. 1 and 2). The fibres in the spindle measure ·025 mm. and ·02 mm. in cross section.

There is a certain amount of increase in the interstitial fat. The intramuscular nerves stain quite well, but there appears to be an increase in the amount of endoneurium. The blood-vessels do not show any marked changes.

By the Marchi method there is seen to be a considerable increase in the amount of interstitial fat. A large number of the muscle-fibres show no change, but others show a well-marked fatty degeneration. This degeneration is a true one, being distributed throughout the whole fibre and not consisting in fat droplets deposited in the neighbourhood of the nucleus. The fatty change is present chiefly in the normal-sized fibres, but it is also seen in some of the atrophic ones, and in some of the small muscular fibres of the muscle spindles.

These changes are all rather more pronounced in the psoas than in the biceps. The diaphragm is almost normal, but pathological changes have commenced, for there is a slight increase in the amount of fibrous tissue, and a few of the small multi-nucleated muscle-fibres are present. The involuntary muscles of the intestines appear quite normal.

The spinal cord was examined by the following methods: Weigert-Pal, Marchi, Nissl and Van Gieson. In the Weigert-Pal sections the whole of the anterolateral part of the cord stains more lightly than the posterior columns, but it is not possible to pick out any particular tract as more definitely affected than the others. The fibres of the anterior root are seen to be much fewer than those of the posterior root, the anterior root being strikingly smaller than the posterior root.

By the Marchi method no recent degeneration was found in the cord, peripheral nerves, posterior or anterior nerve-root, or posterior root ganglia.

The sections stained by Nissl's method showed a most striking diminution in number of the cells of the anterior horn. This diminution affects all parts of the cord, and in the dorsal region contrasts greatly with the cells of Clarke's column. The amount of this diminution is shown by comparing fig. 5—a photograph of the anterior horn of one of the lower lumbar segments—with fig. 6, a photograph of the anterior horn in the same region in a normal child. Fully two-thirds of the cells have disappeared, and the figures also show that the majority of those cells which do remain are considerably smaller than normal. Serial sections of the cervical and lumbar enlargements were examined. It is a rarity to find in these sections cells of the normal size in the anterior cornua, indeed many seem just on the point of complete disappearance. The small cells frequently show an eccentric nucleus, some diminution in the amount of chromatin, and few or no processes. A few cells were found which showed complete chromatolysis; of these the larger number were in the lumbar region, a fact which in all probability fits in with the

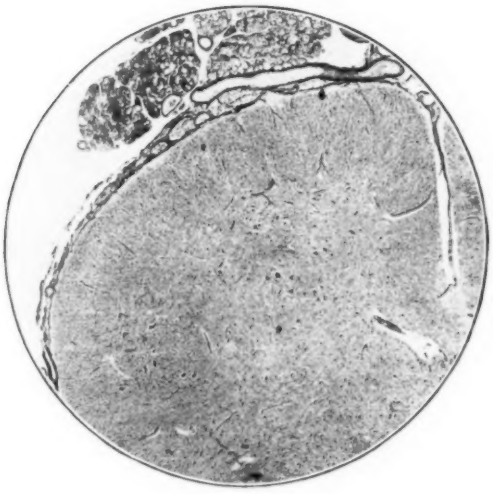

FIG. 5.—Section of anterior horn and anterior nerve root from lower lumbar region stained with hæmatoxylin and Van Gieson's method, showing the great diminution in number and size of the cells of the anterior horn, also the fibrosis and atrophy of the anterior nerve root. Compare with fig. 6.

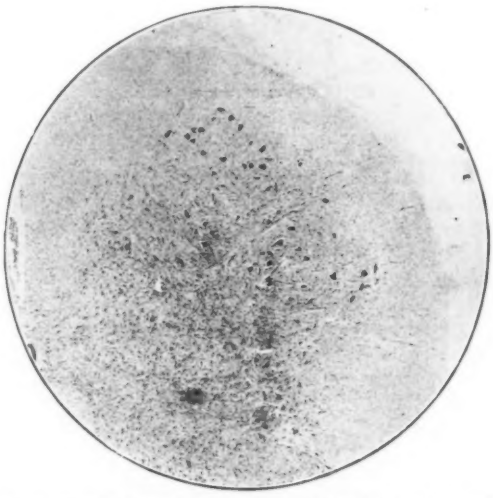

FIG. 6.—Section of anterior horn in the lower lumbar region of a normal child, stained with hæmatoxylin and Van Gieson's method, for comparison with fig. 5.

clinical observation that the increase of paralysis during the last few weeks of life was most apparent in the lower limbs.

The sections stained by Van Gieson's method also showed very well the diminution and atrophy of the anterior cornual cells; in addition they show that there is no overgrowth of the neuroglia in any part of the cord, and that the vessels are normal. The meninges show no change. The size of the anterior roots has been already commented on (*see* fig. 5). They show a considerable increase of fibrous tissue, which contains many fibroblasts, and many of the nerve-fibres take the stain badly. This increase of fibrous tissue has been stated to occur in the intermuscular nerves; it was also found in some of the branches of the brachial plexus examined by this method, but the amount of fibrous tissue was less than that found in the anterior nerve-roots.

The posterior roots and their ganglia were normal by all the methods of examination employed, and so was the medulla.

These pathological findings agree well with those described in the other recorded *post-mortem* examinations on the disease, viz.—great diminution in size and number of the cells of the anterior horn, atrophy of the anterior nerve-roots, fibrosis and atrophy with lipomatosis of the muscles. These findings, while agreeing closely with one of the three *post-mortems* recorded by Batten in his paper, differ from the two younger cases, in the absence of any distinct change by the Marchi method in the anterior roots—intra- and extra-medullary—and in the diminution in the number of cells. In this paper Batten advanced the view that the presence of these Marchi changes in the younger fatal cases, and their absence in the older ones, the presence of little chromatolysis in the younger, and increased chromatolysis and later atrophy of the anterior cornual cells in the older cases, was really due to the severity and duration of the disease; that at a later stage the products of degeneration as shown by the Marchi method became absorbed, whilst the chromatolysis and atrophy of the cells as shown by the Nissl method became more marked. Such an explanation seems to be in all probability the correct one. The slight change observable in our case in the Weigert-Pal sections has also been noticed in other cases (Batten, Werdnig [6], Hoffmann [3]).

## REEFRENCES.

[1] Batten. *Brain*, 1910-1911, vol. xxxiii, p. 433.
[2] Hoffmann. *Deutsche Zeitschr. f. Nervenheilk.*, 1893, Bd. iii, S. 427.
[3] *Idem. Ibid.*, 1897, Bd. ix, S. 264.
[4] *Idem. Ibid.*, 1895, Bd. vi, S. 153.
[5] Thomson and Bruce. *Edin. Hosp. Reports*, 1893, vol. i, p. 361.
[6] Werdnig. *Arch. f. Psychiat.*, 1891, Bd. xxii, S. 437.

## Publications Recently Received.

[*Notes on a book under this heading do not preclude a subsequent review.*]

*La Fonction Cérébelleuse.* Par le Dr. André-Thomas. Pp. 330. Avec 89 figures dans le texte. Paris: Doin et Fils, 1911.

This excellent little book is an attempt to set out clearly the main facts which have emerged from recent work on the structure and functions of the cerebellum. The anatomy is dealt with rather shortly, but the experimental results are treated fully and are followed by a description of the symptoms of cerebellar disease. The last half of the book is devoted to discussion of the significance of these phenomena, and this useful summary is furnished with a good index.

*The Wassermann Sero-Diagnosis of Syphilis in its Application to Psychiatry, Nervous and Mental Disease.* Monograph No. 5. By Dr. Félix Plant. Authorized translation by Smith Ely Jelliffe, M.D., and Louis Casamajor, M.D. Pp. 188. New York: Journal of Nervous and Mental Disease Publishing Company, 1911.

This monograph is an unusually interesting account by one of Professor Wassermann's pupils and fellow-workers of the results obtained with this reaction in cases of cerebral syphilis and parasyphilis. The author begins with a short historical introduction, and, after a chapter devoted to technique, discusses the clinical specificity of the Wassermann reaction. General paralysis, cerebral syphilis, tabo-paresis, and feeble-mindedness on an hereditary syphilitic basis are all discussed quietly and judicially. The results arrived at correspond closely with those enunciated by Neisser and Nonne in Germany and Mott in this country.

*Bericht über die Leistungen auf dem Gebiete der Anatomie des Centralnervensystems,* 1909 und 1910. Von L. Edinger und A. Wallenberg. Bonn: Marcus und Weber, 1912.

This, the seventeenth biennial report on the anatomy of the nervous system which Edinger has edited, is considerably larger than its forerunners, though the number of articles actually reviewed is smaller; this allows a welcome increase in the space devoted to some of the more important. The work has also been more divided up among men who are recognized authorities in the subjects they have undertaken. Brodmann, for instance, deals with the cerebral cortex, H. Vogt with the forebrain, and Röthig has been largely responsible for the sections on comparative anatomy.

As the authors remark, the period included in their review has not been distinguished by any prominent discovery in the anatomy or histology of the nervous system; the most notable feature has been the extending interest in comparative anatomy. The most interesting sections in the report are those on the histology of the nerve cell and fibre, which contain references to over 200 articles; that on the epiphysis and hypophysis, and, finally, the long chapter dealing with comparative anatomy.

The report equals its predecessors in the fair, judicious and critical spirit in which it is written, and it is indispensable to all working at, or interested in, the anatomy and morphology of the nervous system.

*Die Tabes der Frauen.* Von K. MENDEL und E. TOBIAS. Berlin: Karger, 1912.

This monograph is based on the study and analysis of 151 cases of tabes in women. It is chiefly statistical and brings out many points of importance, especially in comparison with tabes in the male sex. However, we think the authors' plea is scarcely made out that its publication is justified by the fact that many of the symptoms of tabes appear differently in the male and female, and that in the latter the disease often bears a special character, One of the most interesting points is the large percentage of cases in which evidence of syphilitic infection can be ascertained by careful examination. Wassermann's reaction too, was positive in 83 per cent. of the cases examined, which is definitely higher than in the male cases investigated during the same period.

*Feeble-mindedness in Children of School Age.* By C. PAGET LAPAGE, M.D. With an appendix on treatment and training, by MARY DENDY, M.A. Pp. 359. Manchester: University Press, 1911.

This book is a simply written account of the natural history of the feeble-minded, more for the practitioner and social worker than for specialists. The relation of the feeble-minded to the State and local authorities is clearly set out and the anti-social danger insisted upon. Various forms of feeble-mindedness are described and illustrated with photographs. Finally, there is an interesting and practical appendix on diet, clothing, and methods of education.

*Diseases of the Nervous System.* By JUDSON S. BURY, M.D., F.R.C.P. Pp. 778. Manchester: University Press, 1912.

A most useful text-book for the senior student and practitioner. The descriptions are short and to the point, and all the recent advances in clinical diagnosis are included. The illustrations are clear and the coloured plates excellent.

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